# Clinical trial results:
# A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial, Conducted Under In-House Blinding Conditions, to Examine the Efficacy and Safety of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Patients

## Summary

| | |
|---|---|
| EudraCT number | 2011-000651-16 |
| Trial protocol | SE PT LT ES NL DK HU SI GR GB IT Outside EU/EEA |
| Global end of trial date | 16 August 2013 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 13 April 2016 |
| First version publication date | 25 February 2015 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 0869-208 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01362530 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | MK-0869: Aprepitant |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Merck Sharp & Dohme Corp |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 16 August 2013 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 16 August 2013 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

This study will compare the safety and efficacy of a three-day oral aprepitant regimen (aprepitant plus ondansetron) to ondansetron alone in the prevention of chemotherapy-induced nausea and vomiting (CINV) in the 120 hours following the initiation of chemotherapy in pediatric participants. Those who complete this first cycle of treatment and meet certain eligibility criteria will have the option of continuing for 5 additional cycles of open-label aprepitant.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

The following additional measure defined for this individual study was in place for the protection of trial subjects:

Subjects were permitted to take "rescue medication" for established (not anticipated) nausea and vomiting throughout the study. Recommended rescue medications included: 5-HT3 antagonists, phenothiazines, butyrophenones, benzamides, corticosteroids, benzodiazepines, and domperidone. In all cases, rescue medication was administered consistent with local regulations and standards of practice.

| | |
|---|---|
| Background therapy: - | |
| Evidence for comparator: - | |
| Actual start date of recruitment | 13 September 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Denmark: 6 |
| Country: Number of subjects enrolled | Greece: 17 |
| Country: Number of subjects enrolled | Italy: 16 |
| Country: Number of subjects enrolled | Netherlands: 17 |
| Country: Number of subjects enrolled | Spain: 20 |
| Country: Number of subjects enrolled | Sweden: 8 |
| Country: Number of subjects enrolled | United Kingdom: 13 |
| Country: Number of subjects enrolled | Lithuania: 11 |
| Country: Number of subjects enrolled | Slovenia: 5 |
| Country: Number of subjects enrolled | Poland: 18 |

| | |
|---|---|
| Country: Number of subjects enrolled | Hungary: 16 |
| Country: Number of subjects enrolled | Russian Federation: 15 |
| Country: Number of subjects enrolled | Korea, Republic of: 25 |
| Country: Number of subjects enrolled | United States: 8 |
| Country: Number of subjects enrolled | Chile: 18 |
| Country: Number of subjects enrolled | Israel: 19 |
| Country: Number of subjects enrolled | Croatia: 9 |
| Country: Number of subjects enrolled | Ecuador: 13 |
| Country: Number of subjects enrolled | Colombia: 11 |
| Country: Number of subjects enrolled | Dominican Republic: 6 |
| Country: Number of subjects enrolled | Peru: 10 |
| Country: Number of subjects enrolled | Argentina: 3 |
| Country: Number of subjects enrolled | Mexico: 4 |
| Country: Number of subjects enrolled | Turkey: 19 |
| Worldwide total number of subjects | 307 |
| EEA total number of subjects | 156 |

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) | 35 |
| Children (2-11 years) | 177 |
| Adolescents (12-17 years) | 95 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The base study consisted of one cycle of treatment (Cycle 1). Participants in either treatment group who met the eligibility criteria were eligible to participate in optional open-label aprepitant treatment for an additional 5 cycles (Cycles 2-6).

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Aprepitant Regimen |

Arm description:

Cycle 1: Participants 12 to 17 years of age, Day 1: aprepitant 125 mg capsule orally (PO) +ondansetron, Days 2 to 3: aprepitant 80 mg capsule PO. Participants 6 months to <12 years of age, Day 1: aprepitant powder for suspension (PFS), 3.0 mg/kg (up to 125 mg) + ondansetron, Days 2 to 3: aprepitant PFS, 2.0 mg/kg (up to 80 mg).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Aprepitant 125 mg |
| Investigational medicinal product code | A04AD12 |
| Other name | MK-0869, Emend |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

On the morning of Day 1: one 125 mg capsule PO 60 minutes prior to chemotherapy for participants 12 to 17 years of age

| | |
|---|---|
| Investigational medicinal product name | Aprepitant 80 mg |
| Investigational medicinal product code | A04AD12 |
| Other name | MK-0869, Emend |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

On the morning of Days 2 and 3: one 80 mg capsule PO for participants 12 to 17 years of age

| | |
|---|---|
| Investigational medicinal product name | Aprepitant powder for suspension (PFS) |
| Investigational medicinal product code | A04AD12 |
| Other name | MK-0869, Emend |
| Pharmaceutical forms | Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

On the morning of Day 1: 3.0 mg/kg (up to 125 mg) PO 60 minutes prior to chemotherapy for participants 6 months to <12 years of age. On the morning of Days 2 and 3: 2.0 mg/kg (up to 80 mg) PO 60 minutes prior to chemotherapy (if applicable) for participants 6 months to <12 years of age

| | |
|---|---|
| Investigational medicinal product name | Ondansetron |
| Investigational medicinal product code | |
| Other name | Zofran |
| Pharmaceutical forms | Capsule, Solution for injection |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

Day 1: Administered according to product label for pediatric usage or local standard of care.

| | |
|---|---|
| Investigational medicinal product name | Emetogenic chemotherapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Any moderately emetic, highly emetic, or very highly emetic chemotherapeutic agent such as cyclophosphamide, doxorubicin, methotrexate, carboplatin, cisplatin, irinotecan, carmustine, ifosfamide, and streptozocin, or chemotherapeutics of a lower emetogenicity that were not previously tolerated. No chemotherapeutic agents were specified by the protocol, and many could potentially have been used.

| | |
|---|---|
| **Arm title** | Control Regimen |

Arm description:

Cycle 1: Participants 12 to 17 years of age, Day 1: dose-matched placebo for aprepitant 125 mg capsule oral (PO) + ondansetron. Days 2 to 3: matching placebo for aprepitant 80 mg capsule PO. Participants 6 months to <12 years of age, Day 1: dose-matched placebo for PFS (3.0 mg/kg, up to 125 mg) + ondansetron. Days 2 to 3:  dose-matched placebo for PFS (2.0 mg/kg, up to 80 mg).

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo for Aprepitant 125 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

On the morning of Day 1: one dose-matched (125 mg) capsule PO 60 minutes prior to chemotherapy for participants 12 to 17 years of age

| | |
|---|---|
| Investigational medicinal product name | Placebo for Aprepitant 80 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

On the morning of Days 2 and 3: one dose-matched (80 mg) capsule PO for participants 12 to 17 years of age

| | |
|---|---|
| Investigational medicinal product name | Placebo for Aprepitant PFS |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

On the morning of Day 1: dose-matched suspension (3.0 mg/kg, up to 125 mg) PO 60 minutes prior to chemotherapy for participants 6 months to <12 years of age. On the morning of Days 2 and 3: dosematched suspension (2.0 mg/kg, up to 80 mg) PO 60 minutes prior to chemotherapy (if applicable) for participants 6 months to <12 years of age.

| | |
|---|---|
| Investigational medicinal product name | Ondansetron |
| Investigational medicinal product code | |
| Other name | Zofran |
| Pharmaceutical forms | Capsule, Solution for injection |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

Day 1: Administered according to product label for pediatric usage or local standard of care.

| | |
|---|---|
| Investigational medicinal product name | Emetogenic chemotherapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Any moderately emetic, highly emetic, or very highly emetic chemotherapeutic agent such as cyclophosphamide, doxorubicin, methotrexate, carboplatin, cisplatin, irinotecan, carmustine, ifosfamide, and streptozocin, or chemotherapeutics of a lower emetogenicity that were not previously tolerated. No chemotherapeutic agents were specified by the protocol, and many could potentially have been used.

| **Number of subjects in period 1** | Aprepitant Regimen | Control Regimen |
|---|---|---|
| Started | 155 | 152 |
| Treated (Intent To Treat Population) | 152 | 150 |
| Completed | 150 | 149 |
| Not completed | 5 | 3 |
| Consent withdrawn by subject | 1 | 2 |
| Physician decision | - | 1 |
| Adverse event, non-fatal | 2 | - |
| Protocol deviation | 2 | - |

## Period 2

| | |
|---|---|
| Period 2 title | Optional Extension (Cycles 2-6) |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| **Arm title** | Open Label Aprepitant (Cycles 2-6) |

Arm description:

Participants completing Cycle 1 from either the aprepitant or the control regimen who met eligibility criteria received open-label aprepitant administered in the same manner as in Cycle 1: Participants 12 to 17 years of age, Day 1: aprepitant 125 mg capsule PO + ondansetron, Days 2 to 3: aprepitant 80 mg capsule PO. Participants 6 months to <12 years of age, Day 1: aprepitant PFS, 3.0 mg/kg (up to 125 mg) + ondansetron, Days 2 to 3: aprepitant PFS, 2.0 mg/kg (up to 80 mg).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Aprepitant 125 mg |
| Investigational medicinal product code | A04AD12 |
| Other name | MK-0869, Emend |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

| | |
|---|---|
| Dosage and administration details: | |
| On the morning of Day 1: one 125 mg capsule PO 60 minutes prior to chemotherapy for participants 12 to 17 years of age | |
| Investigational medicinal product name | Aprepitant 80 mg |
| Investigational medicinal product code | A04AD12 |
| Other name | MK-0869, Emend |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| On the morning of Days 2 and 3: one 80 mg capsule PO for participants 12 to 17 years of age | |
| Investigational medicinal product name | Aprepitant powder for suspension (PFS) |
| Investigational medicinal product code | A04AD12 |
| Other name | MK-0869, Emend |
| Pharmaceutical forms | Oral suspension |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| On the morning of Day 1: 3.0 mg/kg (up to 125 mg) PO 60 minutes prior to chemotherapy for participants 6 months to <12 years of age. On the morning of Days 2 and 3: 2.0 mg/kg (up to 80 mg) PO 60 minutes prior to chemotherapy (if applicable) for participants 6 months to <12 years of age | |
| Investigational medicinal product name | Ondansetron |
| Investigational medicinal product code | |
| Other name | Zofran |
| Pharmaceutical forms | Capsule, Solution for injection |
| Routes of administration | Intravenous use, Oral use |
| Dosage and administration details: | |
| Day 1: Administered according to product label for pediatric usage or local standard of care. | |
| Investigational medicinal product name | Emetogenic chemotherapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Any moderately emetic, highly emetic, or very highly emetic chemotherapeutic agent such as cyclophosphamide, doxorubicin, methotrexate, carboplatin, cisplatin, irinotecan, carmustine, ifosfamide, and streptozocin, or chemotherapeutics of a lower emetogenicity that were not previously tolerated. No chemotherapeutic agents were specified by the protocol, and many could potentially have been used. | |

| **Number of subjects in period 2[1]** | Open Label Aprepitant (Cycles 2-6) |
|---|---|
| Started | 171 |
| Treated | 170 |
| Completed | 46 |
| Not completed | 125 |
| Completed Chemotherapy Regimen | 51 |
| Consent withdrawn by subject | 18 |
| Physician decision | 19 |
| Adverse event, non-fatal | 2 |

| | |
|---|---|
| Did Not Respond To Chemotherapy Regimen | 4 |
| Did Not Meet Additional Criteria | 25 |
| Lost to follow-up | 1 |
| Protocol deviation | 4 |
| Lack of efficacy | 1 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Cycles 2-6 were optional and not required for the study. Following Cycle 1, 171 subjects elected to participate in the optional cycles (Cycles 2-6).

## Baseline characteristics

### Reporting groups

| Reporting group title | Aprepitant Regimen |
|---|---|

Reporting group description:

Cycle 1: Participants 12 to 17 years of age, Day 1: aprepitant 125 mg capsule orally (PO) +ondansetron, Days 2 to 3: aprepitant 80 mg capsule PO. Participants 6 months to <12 years of age, Day 1: aprepitant powder for suspension (PFS), 3.0 mg/kg (up to 125 mg) + ondansetron, Days 2 to 3: aprepitant PFS, 2.0 mg/kg (up to 80 mg).

| Reporting group title | Control Regimen |
|---|---|

Reporting group description:

Cycle 1: Participants 12 to 17 years of age, Day 1: dose-matched placebo for aprepitant 125 mg capsule oral (PO) + ondansetron. Days 2 to 3: matching placebo for aprepitant 80 mg capsule PO. Participants 6 months to <12 years of age, Day 1: dose-matched placebo for PFS (3.0 mg/kg, up to 125 mg) + ondansetron. Days 2 to 3: dose-matched placebo for PFS (2.0 mg/kg, up to 80 mg).

| Reporting group values | Aprepitant Regimen | Control Regimen | Total |
|---|---|---|---|
| Number of subjects | 155 | 152 | 307 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: months | | | |
| arithmetic mean | 97.4 | 99.2 | |
| standard deviation | ± 62.8 | ± 60.8 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 69 | 71 | 140 |
| Male | 86 | 81 | 167 |
| Not recorded | 0 | 0 | 0 |

### Subject analysis sets

| Subject analysis set title | Aprepitant Regimen-Intent-to-treat (ITT) Population |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Aprepitant Regimen ITT population; consisting of all randomized patients who received at least one dose of Aprepitant.

| Subject analysis set title | Control Regimen-ITT Population |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Control Regimen ITT population; consisting of all randomized patients who received at least one dose of control.

| Reporting group values | Aprepitant Regimen-Intent-to-treat (ITT) Population | Control Regimen-ITT Population | |
|---|---|---|---|
| Number of subjects | 152 | 150 | |
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: months | | | |
| arithmetic mean | 97.7 | 99.4 | |
| standard deviation | ± 63.2 | ± 60.9 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 68 | 71 | |
| Male | 84 | 79 | |
| Not recorded | 0 | 0 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Aprepitant Regimen |

Reporting group description:

Cycle 1: Participants 12 to 17 years of age, Day 1: aprepitant 125 mg capsule orally (PO) +ondansetron, Days 2 to 3: aprepitant 80 mg capsule PO. Participants 6 months to <12 years of age, Day 1: aprepitant powder for suspension (PFS), 3.0 mg/kg (up to 125 mg) + ondansetron, Days 2 to 3: aprepitant PFS, 2.0 mg/kg (up to 80 mg).

| | |
|---|---|
| Reporting group title | Control Regimen |

Reporting group description:

Cycle 1: Participants 12 to 17 years of age, Day 1: dose-matched placebo for aprepitant 125 mg capsule oral (PO) + ondansetron. Days 2 to 3: matching placebo for aprepitant 80 mg capsule PO. Participants 6 months to <12 years of age, Day 1: dose-matched placebo for PFS (3.0 mg/kg, up to 125 mg) + ondansetron. Days 2 to 3:  dose-matched placebo for PFS (2.0 mg/kg, up to 80 mg).

| | |
|---|---|
| Reporting group title | Open Label Aprepitant (Cycles 2-6) |

Reporting group description:

Participants completing Cycle 1 from either the aprepitant or the control regimen who met eligibility criteria received open-label aprepitant administered in the same manner as in Cycle 1: Participants 12 to 17 years of age, Day 1: aprepitant 125 mg capsule PO + ondansetron, Days 2 to 3: aprepitant 80 mg capsule PO. Participants 6 months to <12 years of age, Day 1: aprepitant PFS, 3.0 mg/kg (up to 125 mg) + ondansetron, Days 2 to 3: aprepitant PFS, 2.0 mg/kg (up to 80 mg).

| | |
|---|---|
| Subject analysis set title | Aprepitant Regimen-Intent-to-treat (ITT) Population |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Aprepitant Regimen ITT population; consisting of all randomized patients who received at least one dose of Aprepitant.

| | |
|---|---|
| Subject analysis set title | Control Regimen-ITT Population |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Control Regimen ITT population; consisting of all randomized patients who received at least one dose of control.

### Primary: Percentage of Participants with a Complete Response in the Delayed Phase of Cycle 1

| | |
|---|---|
| End point title | Percentage of Participants with a Complete Response in the Delayed Phase of Cycle 1 |

End point description:

The Delayed Phase was defined as 25-120 hours after the start of chemotherapy. Complete response was defined as no vomiting or retching and no use of rescue medication in the delayed phase of Cycle 1.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

25 to 120 hours after the start of chemotherapy (Day 1)

| End point values | Aprepitant Regimen | Control Regimen | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 152 | 150 | | |
| Units: P e r c e n t a g e of participants | | | | |
| number (not applicable) | 50.7 | 26 | | |

### Statistical analyses

| Statistical analysis title | Complete Response in the Delayed Phase of Cycle 1 |
|---|---|

Statistical analysis description:

Cochran-Mantel-Haenszel Analysis: Stratified by age group, use of dexamethasone as an anti-emetic, and receipt of very high risk emetogenic chemotherapy.

| | |
|---|---|
| Comparison groups | Aprepitant Regimen v Control Regimen |
| Number of subjects included in analysis | 302 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[1] |
| P-value | < 0.01 |
| Method | Cochran-Mantel-Haenszel |

Notes:

[1] - The superiority hypotheses was evaluated by comparing the 1-tailed p-value to 0.025 and significance declared if this p-value was ≤0.025.

## Secondary: Percentage of Participants with a Complete Response in the Acute Phase of Cycle 1

| End point title | Percentage of Participants with a Complete Response in the Acute Phase of Cycle 1 |
|---|---|

End point description:

The Acute phase was defined as 0 to 24 hours after the start of chemotherapy. Complete response was defined as no vomiting or retching and no use of rescue medication in the Acute Phase of Cycle 1.

| End point type | Secondary |
|---|---|

End point timeframe:

0 to 24 hours after initiation of chemotherapy (Day 1)

| End point values | Aprepitant Regimen | Control Regimen | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 152 | 150 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 66.4 | 52 | | |

### Statistical analyses

| Statistical analysis title | Complete Response in the Acute Phase of Cycle 1 |
|---|---|

Statistical analysis description:

Cochran-Mantel-Haenszel analysis was stratified by age group, use of dexamethasone as an anti-emetic, and receipt of very high risk emetogenic chemotherapy.

| | |
|---|---|
| Comparison groups | Control Regimen v Aprepitant Regimen |

| | |
|---|---|
| Number of subjects included in analysis | 302 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[2] |
| P-value | < 0.05 |
| Method | Cochran-Mantel-Haenszel |

Notes:

[2] - The superiority hypotheses was evaluated by comparing the 1-tailed p-value to 0.025 and significance declared if this p-value was ≤0.025.

## Secondary: Percentage of Participants with a Complete Response in the Overall Phase of Cycle 1

| | |
|---|---|
| End point title | Percentage of Participants with a Complete Response in the Overall Phase of Cycle 1 |

End point description:

The Overall Phase was defined as 0 to 120 hours after the start of chemotherapy. Complete Response was defined as no vomiting or retching and no use of rescue medication in the Overall Phase of Cycle 1.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

0 to 120 hours after initiation of chemotherapy (Day 1)

| End point values | Aprepitant Regimen | Control Regimen | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 152 | 150 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 40.1 | 20 | | |

### Statistical analyses

| Statistical analysis title | Complete Response in the Overall Phase of Cycle 1 |
|---|---|

Statistical analysis description:

Cochran-Mantel-Haenszel Analysis: Stratified by age group, use of dexamethasone as an anti-emetic, and receipt of very high risk emetogenic chemotherapy.

| | |
|---|---|
| Comparison groups | Aprepitant Regimen v Control Regimen |
| Number of subjects included in analysis | 302 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | < 0.01 |
| Method | Cochran-Mantel-Haenszel |

Notes:

[3] - The superiority hypotheses was evaluated by comparing the 1-tailed p-value to 0.025 and significance declared if this p-value was ≤0.025.

## Secondary: Percentage of Participants with No Vomiting in the Overall Phase of Cycle 1

| | |
|---|---|
| End point title | Percentage of Participants with No Vomiting in the Overall Phase of Cycle 1 |

End point description:

The Overall Phase was defined as 0 to 120 hours after the start of chemotherapy. No vomiting was defined as no emesis or retching or dry heaves in the Overall Phase of Cycle 1.

| End point type | Secondary |
|---|---|

End point timeframe:

0 to 120 hours after initiation of chemotherapy (Day 1)

| **End point values** | Aprepitant Regimen | Control Regimen | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 152 | 150 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 46.7 | 21.3 | | |

**Statistical analyses**

| **Statistical analysis title** | No Vomiting in the Overall Phase of Cycle 1 |
|---|---|

Statistical analysis description:

Cochran-Mantel-Haenszel Analysis: Stratified by age group, use of dexamethasone as an anti-emetic, and receipt of very high risk emetogenic chemotherapy.

| Comparison groups | Aprepitant Regimen v Control Regimen |
|---|---|
| Number of subjects included in analysis | 302 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[4] |
| P-value | < 0.01 |
| Method | Cochran-Mantel-Haenszel |

Notes:

[4] - The superiority hypotheses was evaluated by comparing the 1-tailed p-value to 0.025 and significance declared if this p-value was ≤0.025.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

14 days after the last dose of study drug (for maximum of 6 cycles, up to 6 months)

Adverse event reporting additional description:

Intent-to-treat (ITT) population: all randomized participants who received study medication.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 16.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Aprepitant Regimen Cycle 1 |

Reporting group description:

Cycle 1: Participants 12 to 17 years of age, Day 1: aprepitant 125 mg capsule orally (PO) + ondansetron, Days 2 to 3: aprepitant 80 mg capsule PO. Participants 6 months to <12 years of age, Day 1: aprepitant powder for suspension (PFS), 3.0 mg/kg (up to 125 mg) + ondansetron, Days 2 to 3: aprepitant PFS, 2.0 mg/kg (up to 80 mg).

| | |
|---|---|
| Reporting group title | Aprepitant Regimen Cycles 2-6 |

Reporting group description:

Participants completing Cycle 1 from either the aprepitant or the control regimen who met eligibility criteria received open-label aprepitant administered in the same manner as in Cycle 1: Participants 12 to 17 years of age, Day 1: aprepitant 125 mg capsule orally (PO) + ondansetron, Days 2 to 3: aprepitant 80 mg capsule PO. Participants 6 months to <12 years of age, Day 1: aprepitant powder for suspension (PFS), 3.0 mg/kg (up to 125 mg) + ondansetron, Days 2 to 3: aprepitant PFS, 2.0 mg/kg (up to 80 mg).

| | |
|---|---|
| Reporting group title | Control Regimen Cycle 1 |

Reporting group description:

Cycle 1: Participants 12 to 17 years of age, Day 1: dose-matched placebo for aprepitant 125 mg capsule oral (PO) + ondansetron. Days 2 to 3: matching placebo for aprepitant 80 mg capsule PO. Participants 6 months to <12 years of age, Day 1: dose-matched placebo for PFS (3.0 mg/kg, up to 125 mg) + ondansetron. Days 2 to 3: dose-matched placebo for PFS (2.0 mg/kg, up to 80 mg).

| Serious adverse events | Aprepitant Regimen Cycle 1 | Aprepitant Regimen Cycles 2-6 | Control Regimen Cycle 1 |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 46 / 152 (30.26%) | 84 / 170 (49.41%) | 41 / 150 (27.33%) |
| number of deaths (all causes) | 1 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Epithelioid sarcoma | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Neuroblastoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 170 (0.00%) | 0 / 150 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Osteosarcoma recurrent | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Chills | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 3 / 170 (1.76%) | 2 / 150 (1.33%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |

| | | | |
|---|---|---|---|
| Pyrexia | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 8 / 170 (4.71%) | 2 / 150 (1.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 8 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis in device | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 170 (0.59%) | 0 / 150 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 170 (0.00%) | 0 / 150 (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 |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 170 (0.00%) | 0 / 150 (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 |
| Reproductive system and breast disorders | | | |
| Menorrhagia | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Tracheal inflammation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Drug clearance decreased | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 170 (0.00%) | 0 / 150 (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 |
| Electrocardiogram T wave inversion | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 170 (0.00%) | 0 / 150 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 4 / 170 (2.35%) | 2 / 150 (1.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 1 / 170 (0.59%) | 0 / 150 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 170 (0.00%) | 0 / 150 (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 |
| Injury, poisoning and procedural complications | | | |
| Postoperative wound complication | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |

| | | | |
|---|---|---|---|
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 2 / 170 (1.18%) | 0 / 150 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound dehiscence | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 2 / 170 (1.18%) | 0 / 150 (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 |
| **Nervous system disorders** | | | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 0 / 170 (0.00%) | 1 / 150 (0.67%) |
| 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** | | | |
| Agranulocytosis | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Anaemia | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 9 / 170 (5.29%) | 3 / 150 (2.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 11 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone marrow failure | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 1 / 150 (0.67%) |
| 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 neutropenia | | | |
| subjects affected / exposed | 23 / 152 (15.13%) | 53 / 170 (31.18%) | 22 / 150 (14.67%) |
| occurrences causally related to treatment / all | 0 / 23 | 0 / 88 | 0 / 22 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 2 / 170 (1.18%) | 0 / 150 (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 |
| Neutropenia | | | |
| subjects affected / exposed | 4 / 152 (2.63%) | 4 / 170 (2.35%) | 0 / 150 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 3 / 152 (1.97%) | 4 / 170 (2.35%) | 6 / 150 (4.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 7 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 3 / 170 (1.76%) | 2 / 150 (1.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 170 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Caecitis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 170 (0.00%) | 0 / 150 (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 |
| Duodenitis | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Gastritis erosive | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 8 / 170 (4.71%) | 3 / 150 (2.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 9 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 170 (0.00%) | 0 / 150 (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 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 failure acute | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Infections and infestations | | | |
| Bacillus infection | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 0 / 170 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Balanoposthitis infective | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 0 / 170 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 170 (0.00%) | 0 / 150 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 related infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 152 (1.32%) | 0 / 170 (0.00%) | 0 / 150 (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 |
| Enterobiasis | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Enterococcal sepsis | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Gastroenteritis clostridial | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Otitis media acute | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 170 (0.00%) | 0 / 150 (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 |
| Periorbital cellulitis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 170 (0.00%) | 0 / 150 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 3 / 170 (1.76%) | 2 / 150 (1.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Varicella | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 170 (0.00%) | 0 / 150 (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 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 2 / 170 (1.18%) | 0 / 150 (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 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 3 / 170 (1.76%) | 0 / 150 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 152 (0.00%) | 4 / 170 (2.35%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 170 (0.59%) | 0 / 150 (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 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 0 / 170 (0.00%) | 1 / 150 (0.67%) |
| 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** | Aprepitant Regimen Cycle 1 | Aprepitant Regimen Cycles 2-6 | Control Regimen Cycle 1 |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 106 / 152 (69.74%) | 86 / 170 (50.59%) | 109 / 150 (72.67%) |
| Investigations | | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 8 / 152 (5.26%) | 14 / 170 (8.24%) | 6 / 150 (4.00%) |
| occurrences (all) | 9 | 27 | 7 |
| Platelet count decreased | | | |
| subjects affected / exposed | 10 / 152 (6.58%) | 26 / 170 (15.29%) | 15 / 150 (10.00%) |
| occurrences (all) | 10 | 58 | 16 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 12 / 152 (7.89%) | 32 / 170 (18.82%) | 17 / 150 (11.33%) |
| occurrences (all) | 12 | 83 | 19 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 5 / 152 (3.29%) | 12 / 170 (7.06%) | 6 / 150 (4.00%) |
| occurrences (all) | 5 | 15 | 6 |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Headache | | | |
| subjects affected / exposed | 11 / 152 (7.24%) | 14 / 170 (8.24%) | 7 / 150 (4.67%) |
| occurrences (all) | 11 | 15 | 7 |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 8 / 152 (5.26%) | 13 / 170 (7.65%) | 10 / 150 (6.67%) |
| occurrences (all) | 9 | 22 | 11 |
| Anaemia | | | |
| subjects affected / exposed | 24 / 152 (15.79%) | 62 / 170 (36.47%) | 35 / 150 (23.33%) |
| occurrences (all) | 25 | 134 | 38 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 15 / 152 (9.87%) | 38 / 170 (22.35%) | 14 / 150 (9.33%) |
| occurrences (all) | 15 | 80 | 16 |
| Neutropenia | | | |
| subjects affected / exposed | 17 / 152 (11.18%) | 39 / 170 (22.94%) | 18 / 150 (12.00%) |
| occurrences (all) | 17 | 74 | 20 |
| General disorders and administration site conditions | | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 11 / 170 (6.47%) | 5 / 150 (3.33%) |
| occurrences (all) | 1 | 13 | 5 |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 152 (5.26%) | 22 / 170 (12.94%) | 10 / 150 (6.67%) |
| occurrences (all) | 8 | 27 | 10 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 11 / 152 (7.24%) | 17 / 170 (10.00%) | 10 / 150 (6.67%) |
| occurrences (all) | 15 | 26 | 15 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 10 / 170 (5.88%) | 1 / 150 (0.67%) |
| occurrences (all) | 0 | 12 | 1 |
| Constipation | | | |
| subjects affected / exposed | 3 / 152 (1.97%) | 12 / 170 (7.06%) | 6 / 150 (4.00%) |
| occurrences (all) | 3 | 15 | 6 |
| Diarrhoea | | | |
| subjects affected / exposed | 8 / 152 (5.26%) | 16 / 170 (9.41%) | 8 / 150 (5.33%) |
| occurrences (all) | 11 | 23 | 8 |

| | | | |
|---|---|---|---|
| Nausea | | | |
| subjects affected / exposed | 13 / 152 (8.55%) | 42 / 170 (24.71%) | 17 / 150 (11.33%) |
| occurrences (all) | 20 | 78 | 20 |
| Stomatitis | | | |
| subjects affected / exposed | 5 / 152 (3.29%) | 12 / 170 (7.06%) | 4 / 150 (2.67%) |
| occurrences (all) | 6 | 16 | 4 |
| Vomiting | | | |
| subjects affected / exposed | 21 / 152 (13.82%) | 59 / 170 (34.71%) | 20 / 150 (13.33%) |
| occurrences (all) | 31 | 152 | 21 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 9 / 152 (5.92%) | 18 / 170 (10.59%) | 5 / 150 (3.33%) |
| occurrences (all) | 9 | 25 | 6 |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 152 (1.97%) | 10 / 170 (5.88%) | 3 / 150 (2.00%) |
| occurrences (all) | 3 | 15 | 3 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 11 / 170 (6.47%) | 1 / 150 (0.67%) |
| occurrences (all) | 2 | 11 | 1 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 11 July 2012 | AMENDMENT 02: The primary reason for this amendment is to satisfy requirements proposed by the Food and Drug Administration (FDA) Written Request and to address the aprepitant Chemotherapy-Induced Nausea and Vomiting (CINV) Pediatric Research Equity Act (PREA) requirements. The minimum age requirement for eligibility has been changed to 6 months of age. Patients will be stratified into 4 age groups as follows: 12-17 years; 6 years to < 12 years; 2 years to <6 years; and 6 months to <2 years. |
| 29 August 2012 | AMENDMENT 03: Amendment 02 was immediately replaced with Amendment 03 after an error was discovered in the Cycle 1 Flow Chart. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported