# Clinical trial results:
# A Phase III, Randomized, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of MK-0517/Fosaprepitant and Ondansetron Versus Ondansetron for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Subjects Receiving Emetogenic Chemotherapy

## Summary

| | |
|---|---|
| EudraCT number | 2014-001783-34 |
| Trial protocol | SE NO ES LT FI PT EE HU GB NL GR Outside EU/EEA |
| Global end of trial date | 24 February 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 03 September 2017 |
| First version publication date | 03 September 2017 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 0517-044 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02519842 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Merck Registration Number: MK-0517-044, IND Number: 48,924 |

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 | 24 February 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 24 February 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the efficacy and safety of fosaprepitant (MK-0517) plus ondansetron versus ondansetron alone for the prevention of chemotherapy-induced nausea and vomiting (CINV) in pediatric participants scheduled to receive chemotherapeutic agent(s) associated with moderate or high risk of causing emesis (vomiting), or chemotherapy agent(s) not previously tolerated due to vomiting. The primary hypothesis was that a single dose of fosaprepitant in combination with ondansetron provided superior control of CINV compared to ondansetron alone as measured by the percentage of participants with a Complete Response (no vomiting, no retching, and no use of rescue medications) in the delayed phase (>24 to 120 hours) following initiation of emetogenic chemotherapy in Cycle 1.

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. Participants <12 years of age were not permitted to participate in the current study until Pharmacokinetic/Pharmacodynamic and safety data were evaluated from an earlier study to confirm the planned dose adjustments for subjects <12 years of age.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 14 September 2015 |
| 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 | Chile: 6 |
| Country: Number of subjects enrolled | Colombia: 6 |
| Country: Number of subjects enrolled | Estonia: 1 |
| Country: Number of subjects enrolled | Finland: 3 |
| Country: Number of subjects enrolled | Greece: 10 |
| Country: Number of subjects enrolled | Hungary: 5 |
| Country: Number of subjects enrolled | Korea, Republic of: 14 |
| Country: Number of subjects enrolled | Lithuania: 8 |
| Country: Number of subjects enrolled | Mexico: 2 |
| Country: Number of subjects enrolled | Netherlands: 2 |
| Country: Number of subjects enrolled | Norway: 1 |
| Country: Number of subjects enrolled | Poland: 5 |
| Country: Number of subjects enrolled | Russian Federation: 2 |

| | |
|---|---|
| Country: Number of subjects enrolled | Spain: 7 |
| Country: Number of subjects enrolled | Sweden: 1 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Worldwide total number of subjects | 75 |
| EEA total number of subjects | 45 |

Notes:

**Subjects enrolled per age group**

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 37 |
| Adolescents (12-17 years) | 38 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Eligible participants for chemotherapy Cycles 1-6 were 0-17 years old and had documented malignancies and were scheduled to receive chemotherapeutic agent(s) associated with moderate or high risk of emetogenicity. Participants entering Cycles 2-6 must have completed Cycle 1 and had no unresolved drug related adverse events.

### Pre-assignment

Screening details:

Participants received double-blinded fosaprepitant+ondansetron with/without dexamethasone OR placebo+ondansetron with/without dexamethasone in Cycle 1. Upon completion of Cycle 1, participants from both Cycle 1 arms had the option to continue for up to 5 cycles of open-label fosaprepitant+5-hydroxytryptamine 3 antagonist with/without dexamethasone.

### 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 | Investigator, Subject |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Fosaprepitant Regimen Cycle 1 |

Arm description:

Participants received a single dose of fosaprepitant 150 mg (or age-based adjustment) administered intravenously (IV) on Day 1 prior to chemotherapy plus ondansetron IV on Day 1 prior to chemotherapy and at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. Participants may have also received dexamethasone IV at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Fosaprepitant |
| Investigational medicinal product code | |
| Other name | Emend® for injection fosaprepitant dimeglumine MK-0517 |
| Pharmaceutical forms | Powder for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Single dose of fosaprepitant 150 mg (or age-based adjustment) administered IV on Day 1 prior to chemotherapy

| | |
|---|---|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Dexamethasone administered IV, as specified by local labeling and/or local standard of care, at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy

| | |
|---|---|
| Investigational medicinal product name | Ondansetron |
| Investigational medicinal product code | |
| Other name | Ondansetron hydrochloride Zofran® Injection |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Ondansetron administered IV, as specified by local labeling and/or local standard of care, on Day 1 prior to chemotherapy and at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy

| **Arm title** | Control Regimen Cycle 1 |
|---|---|

Arm description:

Participants received a single dose of matched placebo for fosaprepitant IV on Day 1 prior to chemotherapy plus ondansetron IV on Day 1 prior to chemotherapy and at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. Participants may have also received dexamethasone IV at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo for fosaprepitant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Single dose of Placebo for fosaprepitant administered IV on Day 1 prior to chemotherapy

| | |
|---|---|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Dexamethasone administered IV, as specified by local labeling and/or local standard of care, at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy

| | |
|---|---|
| Investigational medicinal product name | Ondansetron |
| Investigational medicinal product code | |
| Other name | Ondansetron hydrochloride Zofran® Injection |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Ondansetron administered IV, as specified by local labeling and/or local standard of care, on Day 1 prior to chemotherapy and at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy

| **Number of subjects in period 1** | Fosaprepitant Regimen Cycle 1 | Control Regimen Cycle 1 |
|---|---|---|
| Started | 38 | 37 |
| Treated | 37 | 34 |
| Completed | 36 | 34 |
| Not completed | 2 | 3 |
| Non-Compliance with Study Drug | - | 1 |
| Adverse event, non-fatal | 1 | - |
| Screening Failure | 1 | 1 |
| Withdrawn By Parent/Guardian | - | 1 |

## 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** | Fosaprepitant Regimen Cycles 2-6 |

Arm description:

Participants received a single dose of fosaprepitant 150 mg (or age-based adjustment) IV on Day 1 prior to chemotherapy plus a 5-hydroxytryptamine 3 (5-HT3) antagonist on Day 1 prior to chemotherapy and per product label or standard of care. Participants may also have received dexamethasone IV at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Fosaprepitant |
| Investigational medicinal product code | |
| Other name | Emend® for injection fosaprepitant dimeglumine MK-0517 |
| Pharmaceutical forms | Powder for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Single dose of fosaprepitant 150 mg (or age-based adjustment) administered IV on Day 1 prior to chemotherapy

| | |
|---|---|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Dexamethasone administered by a route of administration determined by the investigator, as specified by local labeling and/or local standard of care, at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy

| | |
|---|---|
| Investigational medicinal product name | 5-hydroxytryptamine 3 antagonist |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

5-HT3 antagonist administered by a route of administration determined by the investigator, as specified by local labeling and/or local standard of care, on Day 1 prior to chemotherapy and at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy

| **Number of subjects in period 2[1]** | Fosaprepitant Regimen Cycles 2-6 |
|---|---|
| Started | 55 |
| Completed | 26 |
| Not completed | 29 |
| Consent withdrawn by subject | 1 |
| Physician decision | 5 |
| Did not respond to chemotherapy | 2 |
| Completed chemotherapy | 13 |
| Enrollment Terminated at Site | 1 |
| Adverse event, non-fatal | 1 |
| Death | 1 |
| Withdrawn By Parent/Guardian | 3 |
| Cycle Inclusion/Exclusion Criteria Not Met | 2 |

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: Upon completion of Cycle 1, participants from the fosaprepitant and control arms of Cycle 1 had the option to continue in the fosaprepitant arm in Cycles 2-6.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Fosaprepitant Regimen Cycle 1 |
| Reporting group description: | |
| Participants received a single dose of fosaprepitant 150 mg (or age-based adjustment) administered intravenously (IV) on Day 1 prior to chemotherapy plus ondansetron IV on Day 1 prior to chemotherapy and at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. Participants may have also received dexamethasone IV at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. | |
| Reporting group title | Control Regimen Cycle 1 |
| Reporting group description: | |
| Participants received a single dose of matched placebo for fosaprepitant IV on Day 1 prior to chemotherapy plus ondansetron IV on Day 1 prior to chemotherapy and at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. Participants may have also received dexamethasone IV at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. | |

| Reporting group values | Fosaprepitant Regimen Cycle 1 | Control Regimen Cycle 1 | Total |
|---|---|---|---|
| Number of subjects | 38 | 37 | 75 |
| Age Categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 19 | 18 | 37 |
| Adolescents (12-17 years) | 19 | 19 | 38 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 10.8 | 10.9 | |
| standard deviation | ± 4.2 | ± 4.4 | - |
| Gender Categorical<br>Units: Subjects | | | |
| Female | 14 | 16 | 30 |
| Male | 24 | 21 | 45 |

## End points

### End points reporting groups

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

Reporting group description:

Participants received a single dose of fosaprepitant 150 mg (or age-based adjustment) administered intravenously (IV) on Day 1 prior to chemotherapy plus ondansetron IV on Day 1 prior to chemotherapy and at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. Participants may have also received dexamethasone IV at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy.

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

Reporting group description:

Participants received a single dose of matched placebo for fosaprepitant IV on Day 1 prior to chemotherapy plus ondansetron IV on Day 1 prior to chemotherapy and at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. Participants may have also received dexamethasone IV at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy.

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

Reporting group description:

Participants received a single dose of fosaprepitant 150 mg (or age-based adjustment) IV on Day 1 prior to chemotherapy plus a 5-hydroxytryptamine 3 (5-HT3) antagonist on Day 1 prior to chemotherapy and per product label or standard of care. Participants may also have received dexamethasone IV at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy.

| Subject analysis set title | Fosaprepitant Regimen Cycle 1 |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants received a single dose of fosaprepitant 150 mg (or age-based adjustment) administered intravenously (IV) on Day 1 prior to chemotherapy plus ondansetron IV on Day 1 prior to chemotherapy and at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. Participants may have also received dexamethasone IV at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. Analysis was in the intent-to-treat population which consists of all randomized participants who received any study drug.

| Subject analysis set title | Control Regimen Cycle 1 |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants received a single dose of matched placebo for fosaprepitant IV on Day 1 prior to chemotherapy plus ondansetron IV on Day 1 prior to chemotherapy and at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. Participants may have also received dexamethasone IV at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. Analysis was in the intent-to-treat population which consists of all randomized participants who received any study placebo.

| Subject analysis set title | Fosaprepitant Regimen Cycle 1 |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Participants received a single dose of fosaprepitant 150 mg (or age-based adjustment) administered intravenously (IV) on Day 1 prior to chemotherapy plus ondansetron IV on Day 1 prior to chemotherapy and at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. Participants may have also received dexamethasone IV at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. Analysis was in the all subjects as treated population which consists of all randomized participants who received at least one dose of study drug.

| Subject analysis set title | Control Regimen Cycle 1 |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Participants received a single dose of matched placebo for fosaprepitant IV on Day 1 prior to chemotherapy plus ondansetron IV on Day 1 prior to chemotherapy and at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. Participants may have also received dexamethasone IV at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. Analysis was in the all subjects as treated population which consists of all randomized participants who received at least one dose of study drug.

| | |
|---|---|
| Subject analysis set title | Fosaprepitant Regimen Cycles 2-6 |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Participants received a single dose of fosaprepitant 150 mg (or age-based adjustment) IV on Day 1 prior to chemotherapy plus a 5-hydroxytryptamine 3 (5-HT3) antagonist on Day 1 prior to chemotherapy and per product label or standard of care. Participants may also have received dexamethasone IV at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. Analysis was in the all subjects as treated population which consists of all randomized participants who received at least one dose of study drug.

## Primary: Percentage of Participants Who Experience a Complete Response During the Delayed Phase (>24 to 120 hours post initiation of chemotherapy) in Cycle 1

| | |
|---|---|
| End point title | Percentage of Participants Who Experience a Complete Response During the Delayed Phase (>24 to 120 hours post initiation of chemotherapy) in Cycle 1[1] |

End point description:

Complete Response was defined as no vomiting, no retching, and no use of rescue medication following the initiation of emetogenic chemotherapy in Cycle 1. A vomiting episode was specified as one or more episodes of emesis (expulsion of stomach contents through the mouth) or retching/dry heaves (an attempt to vomit that is not productive of stomach contents). Distinct vomiting episodes were separated by the absence of emesis and retching for at least one minute. The date and time of each vomiting episode was recorded by participants in diaries at the time of occurrence. The percentage of participants with no vomiting and no retching episodes in the delayed phase, defined as the time period of >24 to120 hours post initiation of chemotherapy in Cycle 1, was calculated. The endpoint was based on all participants who received at least 1 dose of study drug during Cycle 1.

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

End point timeframe:

>24 to 120 hours post initiation of chemotherapy (1 to 15 days after the dose of study drug)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Early termination of the study limited the data for efficacy and statistical analyses were not performed for this endpoint.

| **End point values** | Fosaprepitant Regimen Cycle 1 | Control Regimen Cycle 1 | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 37 | 34 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 48.6 | 41.2 | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Participants Who Experience One or More Adverse Events

| | |
|---|---|
| End point title | Percentage of Participants Who Experience One or More Adverse Events |

End point description:

An adverse event (AE) is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not it is considered related to the study drug. The endpoint was based on all participants who received at least 1 dose of study drug during Cycles 1 through 6. An analysis was performed on Tier 2 AEs in Cycle 1 to compare the percentage of participants who received fosaprepitant regimen and experienced at least 1 Tier 2 AE compared with the percentage of participants in the control regimen. The Tier 2 endpoint included broad clinical and laboratory AE categories consisting of the percentage of participants

with any AE, drug-related AE, serious AE, and AEs that are both drug-related and serious. Tier 2 AEs were not pre-specified as events of interest and inclusion in the Tier 2 analysis required that at least 4 participants in any treatment group exhibited the AE.

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

End point timeframe:

Up to 6.5 months (Up to 2 weeks after last dose of study drug)

| **End point values** | Fosaprepitant Regimen Cycle 1 | Control Regimen Cycle 1 | Fosaprepitant Regimen Cycles 2-6 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 37 | 34 | 55 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 89.2 | 79.4 | 78.2 | |

### Statistical analyses

| **Statistical analysis title** | Difference in Percentage of Participants |
|---|---|

Statistical analysis description:

Mean difference in percentage of participants who experienced at least 1 tier 2 AE and received fosaprepitant regimen compared with participants who received control regimen. Estimates were based on the Miettinen & Nurminen method.

| Comparison groups | Fosaprepitant Regimen Cycle 1 v Control Regimen Cycle 1 |
|---|---|
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 9.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.6 |
| upper limit | 27.9 |

## Primary: Percentage of Participants Who Discontinue Study Drug Due to an Adverse Event

| End point title | Percentage of Participants Who Discontinue Study Drug Due to an Adverse Event |
|---|---|

End point description:

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not it is considered related to the study drug. The endpoint was based on all participants who received at least 1 dose of study drug during Cycles 1 through 6. An analysis was performed to compare the percentage of participants who discontinued in Cycle 1 due to an AE and received fosaprepitant regimen compared with the percentage of participants who received control regimen.

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

End point timeframe:

Up to 6 months (Up to last dose of study drug)

| **End point values** | Fosaprepitant Regimen Cycle 1 | Control Regimen Cycle 1 | Fosaprepitant Regimen Cycles 2-6 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 37 | 34 | 55 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 5.4 | 0 | 0 | |

**Statistical analyses**

| **Statistical analysis title** | Difference in Percentage of Participants |
|---|---|

Statistical analysis description:

Mean difference in percentage of participants who discontinued due to an AE and received fosaprepitant regimen compared with participants who received control regimen. Estimates were based on the Miettinen & Nurminen method.

| | |
|---|---|
| Comparison groups | Fosaprepitant Regimen Cycle 1 v Control Regimen Cycle 1 |
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 5.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.1 |
| upper limit | 17.8 |

## Secondary: Percentage of Participants Who Experience a Complete Response During the Acute Phase (0 to 24 hours post initiation of chemotherapy) in Cycle 1

| End point title | Percentage of Participants Who Experience a Complete Response During the Acute Phase (0 to 24 hours post initiation of chemotherapy) in Cycle 1 |
|---|---|

End point description:

Complete Response was defined as no vomiting, no retching, and no use of rescue medication following the initiation of emetogenic chemotherapy in Cycle 1. A vomiting episode was specified as one or more episodes of emesis (expulsion of stomach contents through the mouth) or retching/dry heaves (an attempt to vomit that is not productive of stomach contents). Distinct vomiting episodes were separated by the absence of emesis and retching for at least one minute. The date and time of each vomiting episode was recorded by participants in diaries at the time of occurrence. The percentage of participants with no vomiting and no retching episodes in the acute phase, defined as the time period of 0 to 24 hours post initiation of chemotherapy in Cycle 1, was calculated. The endpoint was based on all participants who received at least 1 dose of study drug during Cycle 1.

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

End point timeframe:

0 to 24 hours post initiation of chemotherapy (up to 1 day after the dose of study drug)

| End point values | Fosaprepitant Regimen Cycle 1 | Control Regimen Cycle 1 | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 37 | 34 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 70.3 | 58.8 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Who Experience a Complete Response During the Overall Phase (0 to 120 hours post initiation of chemotherapy) in Cycle 1

| End point title | Percentage of Participants Who Experience a Complete Response During the Overall Phase (0 to 120 hours post initiation of chemotherapy) in Cycle 1 |
|---|---|

End point description:

Complete Response was defined as no vomiting, no retching, and no use of rescue medication following the initiation of emetogenic chemotherapy in Cycle 1. A vomiting episode was specified as one or more episodes of emesis (expulsion of stomach contents through the mouth) or retching/dry heaves (an attempt to vomit that is not productive of stomach contents). Distinct vomiting episodes were separated by the absence of emesis and retching for at least one minute. The date and time of each vomiting episode was recorded by participants in diaries at the time of occurrence. The percentage of participants with no vomiting and no retching episodes in the overall phase, defined as the time period of 0 to 120 hours post initiation of chemotherapy in Cycle 1, was calculated. The endpoint was based on all participants who received at least 1 dose of study drug during Cycle 1.

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

End point timeframe:

0 to 120 hours post initiation of chemotherapy (up to 15 days after the dose of study drug)

| End point values | Fosaprepitant Regimen Cycle 1 | Control Regimen Cycle 1 | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 37 | 34 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 40.5 | 32.4 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Who Experience No Vomiting, Regardless of

## Rescue Medication Use, During the Overall Phase (0 to 120 hours post initiation of chemotherapy) in Cycle 1

| End point title | Percentage of Participants Who Experience No Vomiting, Regardless of Rescue Medication Use, During the Overall Phase (0 to 120 hours post initiation of chemotherapy) in Cycle 1 |
|---|---|

End point description:

Vomiting was assessed, regardless of rescue medicine use, following the initiation of emetogenic chemotherapy in Cycle 1. A vomiting episode was specified as one or more episodes of emesis (expulsion of stomach contents through the mouth) or retching/dry heaves (an attempt to vomit that is not productive of stomach contents). Distinct vomiting episodes were separated by the absence of emesis and retching for at least one minute. The date and time of each vomiting episode was recorded by participants in diaries at the time of occurrence. Rescue medication was permitted to alleviate symptoms of established nausea or vomiting; but not as preventive medication. The percentage of participants with no vomiting and no retching episodes in the overall phase, defined as the time period of 0 to 120 hours post initiation of chemotherapy in Cycle 1, was calculated. The endpoint was based on all participants who received at least 1 dose of study drug during Cycle 1.

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

End point timeframe:

0 to 120 hours post initiation of chemotherapy (up to 15 days after the dose of study drug)

| **End point values** | Fosaprepitant Regimen Cycle 1 | Control Regimen Cycle 1 | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 37 | 34 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 40.5 | 32.4 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events data were collected up to 6.5 months (from start of study drug and up to 14 days after the last dose for each cycle in Cycles 1-6).

Adverse event reporting additional description:

This safety analysis was based on all participants who received at least 1 dose of study drug during Cycles 1 through 6.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.1 |

### Reporting groups

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

Reporting group description:

Participants received a single dose of fosaprepitant 150 mg (or age-based adjustment) administered intravenously (IV) on Day 1 prior to chemotherapy plus ondansetron IV on Day 1 prior to chemotherapy and at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. Participants may have also received dexamethasone IV at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy.

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

Reporting group description:

Participants received a single dose of fosaprepitant 150 mg (or age-based adjustment) IV on Day 1 prior to chemotherapy plus a 5- hydroxytryptamine 3 (5-HT3) antagonist on Day 1 prior to chemotherapy and per product label or standard of care. Participants may also have received dexamethasone IV at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy.

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

Reporting group description:

Participants received a single dose of matched placebo for fosaprepitant IV on Day 1 prior to chemotherapy plus ondansetron IV on Day 1 prior to chemotherapy and at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy. Participants may have also received dexamethasone IV at investigator's discretion on day(s) of chemotherapy and up to 24 hours after chemotherapy.

| **Serious adverse events** | Fosaprepitant Regimen Cycle 1 | Fosaprepitant Regimen Cycles 2-6 | Control Regimen Cycle 1 |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 11 / 37 (29.73%) | 28 / 55 (50.91%) | 8 / 34 (23.53%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Amylase increased | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 55 (0.00%) | 0 / 34 (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 |
| Cardiac disorders | | | |

| | | | |
|---|---|---|---|
| Tachycardia | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 55 (0.00%) | 0 / 34 (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 | | | |
| Seizure | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 55 (3.64%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone marrow failure | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 3 / 55 (5.45%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 6 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | 19 / 55 (34.55%) | 5 / 34 (14.71%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 32 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 1 / 55 (1.82%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 55 (0.00%) | 0 / 34 (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 |

| | | | |
|---|---|---|---|
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 55 (3.64%) | 0 / 34 (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 |
| General disorders and administration site conditions | | | |
| Complication associated with device | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 0 / 34 (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 |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 55 (0.00%) | 0 / 34 (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 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 55 (3.64%) | 0 / 34 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 0 / 34 (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 |
| Soft tissue inflammation | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 0 / 34 (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 | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 55 (0.00%) | 0 / 34 (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 |
| Gastrointestinal disorders | | | |
| Colitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 0 / 34 (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 |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 0 / 34 (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 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 55 (0.00%) | 0 / 34 (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 | | | |
| Soft tissue mass | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 0 / 34 (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 | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 0 / 34 (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 |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 0 / 34 (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 |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 0 / 34 (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 |
| Influenza | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 0 / 34 (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 bacteraemia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 0 / 34 (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 chronic | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 55 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 55 (3.64%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Product issues | | | |
| Thrombosis in device | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 55 (0.00%) | 0 / 34 (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 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 0 / 34 (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 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 0 / 34 (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 |
| Diet refusal | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 0 / 34 (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 |

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

| Non-serious adverse events | Fosaprepitant Regimen Cycle 1 | Fosaprepitant Regimen Cycles 2-6 | Control Regimen Cycle 1 |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 28 / 37 (75.68%) | 30 / 55 (54.55%) | 18 / 34 (52.94%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 3 / 55 (5.45%) | 3 / 34 (8.82%) |
| occurrences (all) | 2 | 3 | 3 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 2 / 55 (3.64%) | 2 / 34 (5.88%) |
| occurrences (all) | 2 | 3 | 2 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 6 / 37 (16.22%) | 2 / 55 (3.64%) | 3 / 34 (8.82%) |
| occurrences (all) | 6 | 2 | 3 |
| Platelet count decreased | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | 5 / 55 (9.09%) | 3 / 34 (8.82%) |
| occurrences (all) | 4 | 32 | 5 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 11 / 37 (29.73%) | 11 / 55 (20.00%) | 3 / 34 (8.82%) |
| occurrences (all) | 11 | 20 | 3 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 2 / 55 (3.64%) | 2 / 34 (5.88%) |
| occurrences (all) | 1 | 2 | 2 |
| Leukopenia | | | |
| subjects affected / exposed | 5 / 37 (13.51%) | 7 / 55 (12.73%) | 0 / 34 (0.00%) |
| occurrences (all) | 5 | 15 | 0 |
| Neutropenia | | | |
| subjects affected / exposed | 5 / 37 (13.51%) | 4 / 55 (7.27%) | 3 / 34 (8.82%) |
| occurrences (all) | 6 | 5 | 3 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 8 / 37 (21.62%) | 7 / 55 (12.73%) | 2 / 34 (5.88%) |
| occurrences (all) | 8 | 14 | 2 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 2 / 34 (5.88%) |
| occurrences (all) | 0 | 2 | 2 |

| | | | |
|---|---|---|---|
| Mucosal inflammation | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | 4 / 55 (7.27%) | 0 / 34 (0.00%) |
| occurrences (all) | 4 | 6 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | 7 / 55 (12.73%) | 0 / 34 (0.00%) |
| occurrences (all) | 5 | 8 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | 6 / 55 (10.91%) | 1 / 34 (2.94%) |
| occurrences (all) | 4 | 9 | 1 |
| Constipation | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | 5 / 55 (9.09%) | 2 / 34 (5.88%) |
| occurrences (all) | 3 | 6 | 3 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 1 / 55 (1.82%) | 0 / 34 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 9 / 55 (16.36%) | 1 / 34 (2.94%) |
| occurrences (all) | 1 | 14 | 1 |
| Proctalgia | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 3 / 55 (5.45%) | 0 / 34 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 3 / 55 (5.45%) | 0 / 34 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | 11 / 55 (20.00%) | 1 / 34 (2.94%) |
| occurrences (all) | 4 | 24 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 1 / 55 (1.82%) | 0 / 34 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Hiccups | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 0 / 55 (0.00%) | 1 / 34 (2.94%) |
| occurrences (all) | 2 | 0 | 1 |
| Oropharyngeal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 37 (5.41%) | 0 / 55 (0.00%) | 1 / 34 (2.94%) |
| occurrences (all) | 2 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 0 / 55 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 1 / 55 (1.82%) | 1 / 34 (2.94%) |
| occurrences (all) | 2 | 1 | 1 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 55 (1.82%) | 2 / 34 (5.88%) |
| occurrences (all) | 0 | 1 | 2 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 4 / 55 (7.27%) | 1 / 34 (2.94%) |
| occurrences (all) | 2 | 4 | 1 |

## 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.

Enrollment was terminated early because it was determined that data were not necessary to support a claim in pediatric participants. The last participant was enrolled on 2016-08-05. Enrolled participants were allowed to remain active in the study.

Notes: