



## Clinical trial results:

### ONO-7436 Phase III Study–A multicenter, open-label, uncontrolled study for the prevention of chemotherapy-induced nausea and vomiting

#### Summary

EudraCT number	2018-000662-11
Trial protocol	Outside EU/EEA
Global end of trial date	17 February 2011

#### Results information

Result version number	v1 (current)
This version publication date	15 July 2018
First version publication date	15 July 2018

#### Trial information

##### Trial identification

Sponsor protocol code	0869-206
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Number: MK-0869-206, Ono Pharmaceutical Co., Ltd. Protocol Number: ONO 7436-03

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	17 February 2011
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 February 2011
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The objective of the study was to evaluate the safety, efficacy, and pharmacokinetics of aprepitant (MK-0869/ONO-7436) for the prevention of chemotherapy-induced nausea and vomiting (CINV) in pediatric Japanese participants 12-18 years of age with malignant tumor who are scheduled to receive chemotherapy including any of cisplatin, cyclophosphamide, or carboplatin.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 September 2009
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	Japan: 22
Worldwide total number of subjects	22
EEA total number of subjects	0

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	20
Adults (18-64 years)	2
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Japanese participants aged 12-18 years with malignant tumor that is confirmed by cytological or histological examination, who were scheduled to receive chemotherapy including any of cisplatin, cyclophosphamide, or carboplatin.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

<b>Arm title</b>	Aprepitant 125/80
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Arm description:

Participants received aprepitant 125 mg administered orally (PO) plus dexamethasone 4 mg intravenously (IV) and Granisteron 40 mcg/kg administered IV on Day 1 prior to chemotherapy. On Days 2 and 3, participants received aprepitant 80 mg administered PO and dexamethasone 4 mg IV. Granisteron 40 mcg/kg was administered IV on chemotherapy days if highly or moderately emetogenic therapy was administered on Days 1-5.

Arm type	Experimental
Investigational medicinal product name	aprepitant
Investigational medicinal product code	
Other name	EMEND® MK-0869 ONO-7436
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Aprepitant 125 mg was administered orally once a day (QD) on Day 1 prior to chemotherapy followed by 80 mg administered orally QD on Days 2 and 3.

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

Dosage and administration details:

Dexamethasone 4 mg was administered intravenously (IV) once a day on Days 1, 2 and 3 approximately 30 minutes prior to the start of chemotherapy.

Investigational medicinal product name	Granisteron
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Granisteron 40 mcg/kg was administered on Day 1 approximately 30 minutes prior to the start of chemotherapy. In addition if highly or moderately emetogenic therapy was administered on Days 1-5 granisetron 40 mcg/kg was also administered IV on chemotherapy days.

<b>Number of subjects in period 1</b>	Aprepitant 125/80
Started	22
Completed	22

## Baseline characteristics

### Reporting groups

Reporting group title	Aprepitant 125/80
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Reporting group description:

Participants received aprepitant 125 mg administered orally (PO) plus dexamethasone 4 mg intravenously (IV) and Granisteron 40 mcg/kg administered IV on Day 1 prior to chemotherapy. On Days 2 and 3, participants received aprepitant 80 mg administered PO and dexamethasone 4 mg IV. Granisteron 40 mcg/kg was administered IV on chemotherapy days if highly or moderately emetogenic therapy was administered on Days 1-5.

Reporting group values	Aprepitant 125/80	Total	
Number of subjects	22	22	
Age Categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	20	20	
Adults (18-64 years)	2	2	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	15.2		
standard deviation	± 1.7	-	
Gender Categorical			
Units: Subjects			
Female	9	9	
Male	13	13	

## End points

### End points reporting groups

Reporting group title	Aprepitant 125/80
Reporting group description: Participants received aprepitant 125 mg administered orally (PO) plus dexamethasone 4 mg intravenously (IV) and Granisteron 40 mcg/kg administered IV on Day 1 prior to chemotherapy. On Days 2 and 3, participants received aprepitant 80 mg administered PO and dexamethasone 4 mg IV. Granisteron 40 mcg/kg was administered IV on chemotherapy days if highly or moderately emetogenic therapy was administered on Days 1-5.	
Subject analysis set title	Aprepitant 125/80 Efficacy Cohort
Subject analysis set type	Full analysis
Subject analysis set description: The efficacy analysis was in all participants who completed at least 1 dose of study drug.	
Subject analysis set title	Aprepitant 125/80 Safety Cohort
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis was in all participants who completed at least 1 dose of study drug.	
Subject analysis set title	Aprepitant 125/80 PK Cohort
Subject analysis set type	Sub-group analysis
Subject analysis set description: The PK analysis was in all participants who completed at least 1 dose of study drug according to protocol and had adequate data available for the PK parameter being analyzed.	

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

End point title	Percentage of Participants Who Experience a Complete Response During the Overall Phase (0 to 120 hours post initiation of chemotherapy) <sup>[1]</sup>
End point description: Complete response was defined as no vomiting and no use of rescue medication following the initiation of emetogenic chemotherapy. A vomiting episode was specified as one or more continuous vomits (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 vomiting and retching for at least one minute. The date, time, and number of vomiting episodes were recorded by participants in diaries at the time of occurrence. The endpoint analysis was in all participants who completed at least 1 dose of study drug. The percentage of participants with vomiting and no use of rescue medication in the overall phase, defined as the time period of 0 to 120 hours post initiation of chemotherapy, was calculated and presented with two-sided 95% confidence intervals calculated by the Clopper-Pearson exact method.	
End point type	Primary
End point timeframe: 0 to 120 hours post initiation of chemotherapy	

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: No statistical analyses were planned for this endpoint.

End point values	Aprepitant 125/80 Efficacy Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of participants				
number (confidence interval 95%)	45.5 (24.4 to 67.8)			

## Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants Who Experience a Complete Response During the Acute Phase (0 to 24 hours post initiation of chemotherapy) <sup>[2]</sup>
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#### End point description:

Complete response was defined as no vomiting and no use of rescue medication following the initiation of emetogenic chemotherapy. A vomiting episode was specified as one or more continuous vomits (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 vomiting and retching for at least one minute. The date, time, and number of vomiting episodes were recorded by participants in diaries at the time of occurrence. The endpoint analysis was in all participants who completed at least 1 dose of study drug. The percentage of participants with vomiting and no use of rescue medication in the acute phase, defined as the time period of 0 to 24 hours post initiation of chemotherapy, was calculated and presented with two-sided 95% confidence intervals calculated by the Clopper-Pearson exact method.

End point type	Primary
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#### End point timeframe:

0 to 24 hours post initiation of chemotherapy

#### Notes:

[2] - 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: No statistical analyses were planned for this endpoint.

<b>End point values</b>	Aprepitant 125/80 Efficacy Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of participants				
number (confidence interval 95%)	68.2 (45.1 to 86.1)			

## Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants Who Experience a Complete Response During the Delayed Phase (>24 to 120 hours post initiation of chemotherapy) <sup>[3]</sup>
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#### End point description:

Complete response was defined as no vomiting and no use of rescue medication following the initiation

of emetogenic chemotherapy. A vomiting episode was specified as one or more continuous vomits (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 vomiting and retching for at least one minute. The date, time, and number of vomiting episodes were recorded by participants in diaries at the time of occurrence. The endpoint analysis was in all participants who completed at least 1 dose of study drug. The percentage of participants with vomiting and no use of rescue medication in the delayed phase, defined as the time period of >24 to 120 hours post initiation of chemotherapy, was calculated and presented with two-sided 95% confidence intervals calculated by the Clopper-Pearson exact method.

End point type	Primary
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End point timeframe:

>24 to 120 hours post initiation of chemotherapy

Notes:

[3] - 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: No statistical analyses were planned for this endpoint.

<b>End point values</b>	Aprepitant 125/80 Efficacy Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of participants				
number (confidence interval 95%)	59.1 (36.4 to 79.3)			

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Participants Who Experience One or More Drug-related AE

End point title	Percentage of Participants Who Experience One or More Drug-related AE <sup>[4]</sup>
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End point description:

A drug-related AE was an AE that was determined by the investigator to be related to the treatment. The endpoint analysis was in all participants who completed at least 1 dose of study drug. The percentage of participants who experienced at least one drug-related AE was calculated and presented with two-sided 95% confidence intervals calculated by the Clopper-Pearson exact method.

End point type	Primary
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End point timeframe:

up to 15 days after the start of study treatment

Notes:

[4] - 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: No statistical analyses were planned for this endpoint.

<b>End point values</b>	Aprepitant 125/80 Safety Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of participants				
number (confidence interval 95%)	4.5 (0.1 to 22.8)			



## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants Who Discontinued Study Drug Due to a Drug-related AE

End point title	Percentage of Participants Who Discontinued Study Drug Due to a Drug-related AE <sup>[5]</sup>
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End point description:

The endpoint analysis was in all participants who completed at least 1 dose of study drug. The percentage of participants who discontinued study treatment due to a drug-related AE was calculated and presented with two-sided 95% confidence intervals calculated by the Clopper-Pearson exact method.

End point type	Primary
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End point timeframe:

up to 5 days

Notes:

[5] - 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: No statistical analyses were planned for this endpoint.

<b>End point values</b>	Aprepitant 125/80 Safety Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 15.4)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Who Experience Total Control During the Overall Phase (0 to 120 hours post initiation of chemotherapy)

End point title	Percentage of Participants Who Experience Total Control During the Overall Phase (0 to 120 hours post initiation of chemotherapy)
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End point description:

Total control was defined as no vomiting, no nausea, and no use of rescue medication following the initiation of emetogenic chemotherapy. A vomiting episode was specified as one or more continuous vomits (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 vomiting and retching for at least one minute. The date, time, and number of vomiting episodes were recorded by participants in diaries at the time of occurrence. The endpoint analysis was in all participants who completed at least 1 dose of study drug. The percentage of participants with no vomiting, no nausea, and no use of rescue medication in the overall phase, defined as the time period of

0 to 120 hours post initiation of chemotherapy, was calculated and presented with two-sided 95% confidence intervals calculated by the Clopper-Pearson exact method.

End point type	Secondary
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End point timeframe:

0 to 120 hours post initiation of chemotherapy

<b>End point values</b>	Aprepitant 125/80 Efficacy Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of participants				
number (confidence interval 95%)	40.9 (20.7 to 63.6)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with No Vomiting During the Overall Phase (0 to 120 hours post initiation of chemotherapy)

End point title	Percentage of Participants with No Vomiting During the Overall Phase (0 to 120 hours post initiation of chemotherapy)
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End point description:

Vomiting was assessed, regardless of rescue medicine use for treatment of emergent nausea and vomiting, following chemotherapy. A vomiting episode was specified as one or more continuous vomits (expulsion of stomach contents through the mouth) or retching/dry heaves (an attempt to vomit that is not productive of stomach contents). Vomiting episodes were separated by the absence of vomiting/retching for  $\geq 1$  minute. The date, time, and number of vomiting episodes were recorded by participants in diaries at the time of occurrence. Rescue medication was permitted for emergent nausea or vomiting but not as preventive medication. The endpoint analysis was in all participants who completed at least 1 dose of study drug. The percentage of participants with no vomiting episodes in the overall phase, defined as the time period of 0-120 hours post initiation of chemotherapy, was calculated and presented with two-sided 95% confidence intervals calculated by the Clopper-Pearson exact method.

End point type	Secondary
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End point timeframe:

0 to 120 hours post initiation of chemotherapy

<b>End point values</b>	Aprepitant 125/80 Efficacy Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of participants				
number (confidence interval 95%)	63.6 (40.7 to 82.8)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with No Vomiting During the Acute Phase (0 to 24 hours post initiation of chemotherapy)

End point title	Percentage of Participants with No Vomiting During the Acute Phase (0 to 24 hours post initiation of chemotherapy)
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End point description:

Vomiting was assessed, regardless of rescue medicine use for treatment of emergent nausea and vomiting, following chemotherapy. A vomiting episode was specified as one or more continuous vomits (expulsion of stomach contents through the mouth) or retching/dry heaves (an attempt to vomit that is not productive of stomach contents). Vomiting episodes were separated by the absence of vomiting/retching for  $\geq 1$  minute. The date, time, and number of vomiting episodes were recorded by participants in diaries at the time of occurrence. Rescue medication was permitted for emergent nausea or vomiting but not as preventive medication. The endpoint analysis was in all participants who completed at least 1 dose of study drug. The percentage of participants with no vomiting episodes in the acute phase, defined as the time period of 0-24 hours post initiation of chemotherapy, was calculated and presented with two-sided 95% confidence intervals calculated by the Clopper-Pearson exact method.

End point type	Secondary
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End point timeframe:

0 to 24 hours post initiation of chemotherapy

<b>End point values</b>	Aprepitant 125/80 Efficacy Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of participants				
number (confidence interval 95%)	72.7 (49.8 to 89.3)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with No Vomiting During the Delayed Phase (>24 to 120 hours post initiation of chemotherapy)

End point title	Percentage of Participants with No Vomiting During the Delayed Phase (>24 to 120 hours post initiation of chemotherapy)
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End point description:

Vomiting was assessed, regardless of rescue medicine use for treatment of emergent nausea and vomiting, following chemotherapy. A vomiting episode was specified as one or more continuous vomits (expulsion of stomach contents through the mouth) or retching/dry heaves (an attempt to vomit that is

not productive of stomach contents). Vomiting episodes were separated by the absence of vomiting/retching for  $\geq 1$  minute. The date, time, and number of vomiting episodes were recorded by participants in diaries at the time of occurrence. Rescue medication was permitted for emergent nausea or vomiting but not as preventive medication. The endpoint analysis was in all participants who completed at least 1 dose of study drug. The percentage of participants with no vomiting episodes in the delayed phase, defined as the time period of >24-120 hours post initiation of chemotherapy, was calculated and presented with two-sided 95% confidence intervals calculated by the Clopper-Pearson exact method.

End point type	Secondary
End point timeframe:	
>24 to 120 hours post initiation of chemotherapy	

<b>End point values</b>	Aprepitant 125/80 Efficacy Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of participants				
number (confidence interval 95%)	72.7 (49.8 to 89.3)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with No Use of Rescue Therapy During the Overall Phase (0 to 120 hours post initiation of chemotherapy)

End point title	Percentage of Participants with No Use of Rescue Therapy During the Overall Phase (0 to 120 hours post initiation of chemotherapy)
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End point description:

Rescue therapy was allowed for treatment of emergent nausea and vomiting following the initiation of emetogenic chemotherapy but was restricted to permitted medications only. The endpoint analysis was in all participants who completed at least 1 dose of study drug. The percentage of participants with no use of rescue therapy in the overall phase, defined as the time period of 0 to 120 hours post initiation of chemotherapy, was calculated and presented with two-sided 95% confidence intervals calculated by the Clopper-Pearson exact method.

End point type	Secondary
End point timeframe:	
0 to 120 hours post initiation of chemotherapy	

<b>End point values</b>	Aprepitant 125/80 Efficacy Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of participants				
number (confidence interval 95%)	59.1 (36.4 to 79.3)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with No Use of Rescue Therapy During the Acute Phase (0 to 24 hours post initiation of chemotherapy)

End point title	Percentage of Participants with No Use of Rescue Therapy During the Acute Phase (0 to 24 hours post initiation of chemotherapy)
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#### End point description:

Rescue therapy was allowed for treatment of emergent nausea and vomiting following the initiation of emetogenic chemotherapy but was restricted to permitted medications only. The endpoint analysis was in all participants who completed at least 1 dose of study drug. The percentage of participants with no use of rescue therapy in the acute phase, defined as the time period of 0 to 24 hours post initiation of chemotherapy, was calculated and presented with two-sided 95% confidence intervals calculated by the Clopper-Pearson exact method.

End point type	Secondary
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#### End point timeframe:

0 to 24 hours post initiation of chemotherapy

<b>End point values</b>	Aprepitant 125/80 Efficacy Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of participants				
number (confidence interval 95%)	81.8 (59.7 to 94.8)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with No Use of Rescue Therapy During the Delayed Phase (>24 to 120 hours post initiation of chemotherapy)

End point title	Percentage of Participants with No Use of Rescue Therapy During the Delayed Phase (>24 to 120 hours post initiation of chemotherapy)
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#### End point description:

Rescue therapy was allowed for treatment of emergent nausea and vomiting following the initiation of emetogenic chemotherapy but was restricted to permitted medications only. The endpoint analysis was in all participants who completed at least 1 dose of study drug. The percentage of participants with no use of rescue therapy in the delayed phase, defined as the time period of >24 to 120 hours post initiation of chemotherapy, was calculated and presented with two-sided 95% confidence intervals calculated by the Clopper-Pearson exact method.

End point type	Secondary
End point timeframe:	
>24 to 120 hours post initiation of chemotherapy	

<b>End point values</b>	Aprepitant 125/80 Efficacy Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of participants				
number (confidence interval 95%)	72.7 (49.8 to 89.3)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with No Nausea During the Overall Phase (0 to 120 hours post initiation of chemotherapy)

End point title	Percentage of Participants with No Nausea During the Overall Phase (0 to 120 hours post initiation of chemotherapy)
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End point description:

In this study, nausea was defined as significant nausea that may interfere with usual daily activities. Nausea was determined by an investigator inquiry. The endpoint analysis was in all participants who completed at least 1 dose of study drug. The percentage of participants with no nausea in the overall phase, defined as the time period of 0 to 120 hours post initiation of chemotherapy, was calculated and presented with two-sided 95% confidence intervals calculated by the Clopper-Pearson exact method.

End point type	Secondary
End point timeframe:	
0 to 120 hours post initiation of chemotherapy	

<b>End point values</b>	Aprepitant 125/80 Efficacy Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of participants				
number (confidence interval 95%)	50.0 (28.2 to 71.8)			

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Who Experience One or More Adverse Events (AE)

End point title	Percentage of Participants Who Experience One or More Adverse Events (AE)
End point description: An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship to the treatment. An AE was any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product/protocol-specified procedure, whether or not considered related to the medicinal product/protocol-specified procedure. Any worsening of a preexisting condition temporally associated with the use of the product was also an AE. The endpoint analysis was in all participants who completed at least 1 dose of study drug. The percentage of participants who experienced at least one AE was calculated and presented with two-sided 95% confidence intervals calculated by the Clopper-Pearson exact method.	
End point type	Secondary
End point timeframe: up to 15 days after the start of study treatment	

End point values	Aprepitant 125/80 Safety Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of participants				
number (confidence interval 95%)	100.0 (84.6 to 100.0)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Observed Maximum Concentration (Cmax) of Aprepitant

End point title	Observed Maximum Concentration (Cmax) of Aprepitant
End point description: Blood samples were obtained at specified time points for the pharmacokinetic (PK) analysis of Cmax of aprepitant. Aprepitant concentrations were calculated using non-compartment analysis methods. The endpoint analysis was in all participants who completed at least 1 dose of study drug according to protocol and had adequate data available for the PK parameter being analyzed. The Cmax of aprepitant after oral administration is presented.	
End point type	Secondary
End point timeframe: Day 1: 1, 2, 3, 5, 9, and 11 hours postdose; Day 2: predose; Days 3 and 4: predose and 24 hours postdose	

<b>End point values</b>	Aprepitant 125/80 PK Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: ng/mL				
arithmetic mean (standard deviation)	2350 (± 920)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Maximum Concentration (Tmax) of Aprepitant

End point title	Time to Maximum Concentration (Tmax) of Aprepitant
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End point description:

Blood samples were obtained at specified time points for the PK analysis of Tmax of aprepitant. Aprepitant concentrations were calculated using non-compartment analysis methods. The endpoint analysis was in all participants who completed at least 1 dose of study drug according to protocol and had adequate data available for the PK parameter being analyzed. The Tmax of aprepitant after oral administration is presented.

End point type	Secondary
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End point timeframe:

Day 1: 1, 2, 3, 5, 9, and 11 hours postdose; Day 2: predose; Days 3 and 4: predose and 24 hours postdose

<b>End point values</b>	Aprepitant 125/80 PK Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: hours				
arithmetic mean (full range (min-max))	5.0 (2.0 to 24.0)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Concentration-time Curve of Aprepitant From Time 0 to 24 Hours (AUC 0-24h)

End point title	Area Under the Concentration-time Curve of Aprepitant From Time 0 to 24 Hours (AUC 0-24h)
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End point description:

Blood samples were obtained at specified time points for the PK analysis of AUC 0-24h of aprepitant. Aprepitant concentrations were calculated using non-compartment analysis methods. The endpoint analysis was in all participants who completed at least 1 dose of study drug according to protocol and had adequate data available for the PK parameter being analyzed. The AUC 0-24h of aprepitant after oral administration is presented.



End point type	Secondary
End point timeframe:	
Day 1: 1, 2, 3, 5, 9, and 11 hours postdose; Day 2: predose; Days 3 and 4: predose and 24 hours postdose	

<b>End point values</b>	Aprepitant 125/80 PK Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: ng•h/mL				
arithmetic mean (standard deviation)	28100 (± 10400)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Concentration of Aprepitant After 24 Hours (C24h)

End point title	Plasma Concentration of Aprepitant After 24 Hours (C24h)
End point description:	
Blood samples were obtained at specified time points for the PK analysis of C24h of aprepitant. Aprepitant concentrations were calculated using non-compartment analysis methods. The endpoint analysis was in all participants who completed at least 1 dose of study drug according to protocol and had adequate data available for the PK parameter being analyzed. The C24h of aprepitant after oral administration is presented.	
End point type	Secondary
End point timeframe:	
Day 1: 1, 2, 3, 5, 9, and 11 hours postdose; Day 2: predose; Days 3 and 4: predose and 24 hours postdose	

<b>End point values</b>	Aprepitant 125/80 PK Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: ng/mL				
arithmetic mean (standard deviation)	675 (± 482)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Concentration of Aprepitant After 48 Hours (C48h)

End point title	Plasma Concentration of Aprepitant After 48 Hours (C48h)
End point description:	
Blood samples were obtained at specified time points for the PK analysis of C48h of aprepitant. Aprepitant concentrations were calculated using non-compartment analysis methods. The endpoint analysis was in all participants who completed at least 1 dose of study drug according to protocol and had adequate data available for the PK parameter being analyzed. The C48h of aprepitant after oral administration is presented.	
End point type	Secondary
End point timeframe:	
Day 1: 1, 2, 3, 5, 9, and 11 hours postdose; Day 2: predose; Days 3 and 4: predose and 24 hours postdose	

<b>End point values</b>	Aprepitant 125/80 PK Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: ng/mL				
arithmetic mean (standard deviation)	492 (± 408)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Concentration of Aprepitant After 72 Hours (C72h)

End point title	Plasma Concentration of Aprepitant After 72 Hours (C72h)
End point description:	
Blood samples were obtained at specified time points for the PK analysis of C72h of aprepitant. Aprepitant concentrations were calculated using non-compartment analysis methods. The endpoint analysis was in all participants who completed at least 1 dose of study drug according to protocol and had adequate data available for the PK parameter being analyzed. The C72h of aprepitant after oral administration is presented.	
End point type	Secondary
End point timeframe:	
Day 1: 1, 2, 3, 5, 9, and 11 hours postdose; Day 2: predose; Days 3 and 4: predose and 24 hours postdose	

<b>End point values</b>	Aprepitant 125/80 PK Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: ng/mL				
arithmetic mean (standard deviation)	603 (± 608)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Who Discontinued Study Drug Due to an AE

End point title	Percentage of Participants Who Discontinued Study Drug Due to an AE
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End point description:

The endpoint analysis was in all participants who completed at least 1 dose of study drug. The percentage of participants who discontinued study treatment due to an AE was calculated and presented with two-sided 95% confidence intervals calculated by the Clopper-Pearson exact method.

End point type	Secondary
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End point timeframe:

up to 5 days

<b>End point values</b>	Aprepitant 125/80 Safety Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of participants				
number (confidence interval 95%)	0 (0.0 to 15.4)			

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

up to 15 days after the start of study treatment

Adverse event reporting additional description:

The safety population included all participants that received at least 1 dose of aprepitant.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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### Reporting groups

Reporting group title	Aprepitant 125/80 Safety Cohort
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Reporting group description:

Participants received aprepitant (MK-0869/ONO -7436) 125 mg administered orally (PO) plus dexamethasone 4 mg intravenously (IV) and Granisteron 40 mcg/kg administered IV on Day 1 prior to chemotherapy. On Days 2 and 3, participants received aprepitant (MK-0869/ONO -7436) 80 mg administered PO and dexamethasone 4 mg IV. Granisteron 40 mcg/kg was administered IV on chemotherapy days if highly or moderately emetogenic therapy was administered on further days. The safety analysis was in all participants who completed at least 1 dose of study drug.

Serious adverse events	Aprepitant 125/80 Safety Cohort		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 22 (9.09%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Mucous membrane disorder			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Aprepitant 125/80 Safety Cohort		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Blood potassium decreased			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Blood sodium decreased			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	6		
Blood urea increased			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	4		
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Glucose urine present			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Haematocrit decreased			
subjects affected / exposed	11 / 22 (50.00%)		
occurrences (all)	12		
Haemoglobin decreased			
subjects affected / exposed	13 / 22 (59.09%)		
occurrences (all)	15		
Lymphocyte count decreased			
subjects affected / exposed	18 / 22 (81.82%)		
occurrences (all)	18		
Neutrophil count decreased			

subjects affected / exposed occurrences (all)	21 / 22 (95.45%) 21		
Neutrophil count increased subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Platelet count decreased subjects affected / exposed occurrences (all)	18 / 22 (81.82%) 18		
Red blood cell count decreased subjects affected / exposed occurrences (all)	12 / 22 (54.55%) 13		
Weight decreased subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
White blood cell count decreased subjects affected / exposed occurrences (all)	20 / 22 (90.91%) 20		
White blood cell count increased subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Protein urine present subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	4 / 22 (18.18%) 4		
Febrile neutropenia subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
General disorders and administration site conditions			

Malaise subjects affected / exposed occurrences (all)	11 / 22 (50.00%) 12		
Pyrexia subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3		
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Constipation subjects affected / exposed occurrences (all)	4 / 22 (18.18%) 5		
Nausea subjects affected / exposed occurrences (all)	10 / 22 (45.45%) 10		
Stomatitis subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3		
Vomiting subjects affected / exposed occurrences (all)	5 / 22 (22.73%) 6		
Respiratory, thoracic and mediastinal disorders			
Epistaxis subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Hiccups subjects affected / exposed occurrences (all)	4 / 22 (18.18%) 5		
Skin and subcutaneous tissue disorders			
Dermatitis subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Erythema subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		

Urticaria subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	11 / 22 (50.00%) 13		



## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported