Clinical trial results:
A phase 3, multicenter, randomized, double-blind, active control study to evaluate the safety and efficacy of IV pro-netupitant/palonosetron (260 mg/0.25 mg) combination for the prevention of chemotherapy-induced nausea and vomiting in repeated chemotherapy cycles in patients receiving highly emetogenic chemotherapy

Summary

EudraCT number	2015-001800-74
Trial protocol	AT DE CZ ES PL HR
Global end of trial date	02 August 2016

Results information

Result version number	v1 (current)
This version publication date	02 December 2017
First version publication date	02 December 2017

Trial information

Trial identification

Sponsor protocol code	NEPA-15-18

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02517021
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Helsinn Healthcare SA
Sponsor organisation address	Via Pian Scairolo 9, Lugano, Switzerland, 6912
Public contact	Clinical Operation, Helsinn Healthcare SA, +41 91 985 21 21, daniel.voisin@helsinn.com
Scientific contact	Clinical Operation, Helsinn Healthcare SA, +41 91 985 21 21, daniel.voisin@helsinn.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 August 2016
Global end of trial reached?	Yes
Global end of trial date	02 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the safety and tolerability of a single dose of intravenous fosnetupitant/palonosetron (260 mg/0.25 mg) fixed-dose combination (IV NEPA FDC) infused over 30 minutes (min), with Oral dexamethasone, in initial and repeated cycles of highly emetogenic chemotherapy (HEC).

Protection of trial subjects:

This study was in compliance with the ethical principles founded in the Declaration of Helsinki, the International Conference on Harmonisation (ICH) guidelines regarding Good Clinical Practices and the European Union Directives on Clinical Trials. The appropriateness of the clinical trial protocol as well as the risks and benefits to study participants were approved by the relevant IECs/IRBs.
In addition, an independent Data Safety Monitoring Board (DSMB) was convened for the evaluation of safety data during the study in order to perform a qualitative safety assessment.

Background therapy:

Oral dexamethasone

Evidence for comparator: -

Actual start date of recruitment	17 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Serbia: 55
Country: Number of subjects enrolled	Ukraine: 162
Country: Number of subjects enrolled	United States: 12
Country: Number of subjects enrolled	Poland: 113
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Croatia: 23
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	Germany: 5
Worldwide total number of subjects	405
EEA total number of subjects	174

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)	0
Adults (18-64 years)	262
From 65 to 84 years	143
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult chemotherapy-naïve (at study entry) male or female patients with a diagnosis of malignant solid tumor requiring treatment with one of the reference HEC regimens on Day 1 of each cycle. Patients were enrolled in 56 study centers in 11 countries.

Pre-assignment

Screening details:

A total of 400 patients (200 per treatment group) were planned to be randomized in the study. A total of 405 patients who met the inclusion criteria were eventually randomized. Of the 405 patients randomized, only one randomized patient in the Oral NEPA FDC group did not receive active study drug and reference HEC and was excluded from all analysis

Period 1

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

Blinding implementation details:

The blinding of the study drugs was guaranteed by the use of identical placebos to the respective active drugs (double-dummy technique). When Oral NEPA FDC capsule was administered to subjects of the control group, a placebo capsule was administered to subjects of the test group. When IV NEPA FDC infusion was administered to subjects of the test group, an IV infusion of placebo was administered to subjects of the control group.

Arms

Are arms mutually exclusive?	Yes
Arm title	IV NEPA FDC

Arm description:

IV fosnetupitant/palonosetron (260 mg/0.25 mg) FDC (IV NEPA FDC) was to be administered as a 30-min infusion of a 50-mL solution on Day 1 of each cycle. The 30-min (±5 min) IV NEPA FDC infusion was to be started 30 min prior to the start of the reference chemotherapy administration. The 30-min IV infusion was to be completed before starting chemotherapy administration.

Arm type	Experimental
Investigational medicinal product name	IV fosnetupitant/palonosetron fixed-dose combination for infusion (IV NEPA FDC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV infusion of 30 min duration to begin 30 min prior to the start of reference chemotherapy administration.

Arm title	Oral NEPA FDC

Arm description:

Oral netupitant/palonosetron (300 mg/0.50 mg) FDC (Oral NEPA FDC) was to be administered on Day 1 of each cycle. Oral NEPA FDC capsule was to be administered 60 min prior to the start of the reference chemotherapy administration.

Arm type	Active comparator

Investigational medicinal product name	Oral netupitant/palonosetron fixed-dose combination (Oral NEPA FDC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

300 mg netupitant/0.50 mg palonosetron. To be administered 60 min prior to the start of reference chemotherapy administration

Number of subjects in period 1	IV NEPA FDC	Oral NEPA FDC
Started	203	202
Completed	120	117
Not completed	83	85
Consent withdrawn by subject	8	7
Physician decision	8	12
Adverse event, non-fatal	16	18
Death	10	15
I/E criteria not met for a repeated cycle	10	5
Overall study closure	24	19
Other reasons	5	6
Lost to follow-up	2	3

Baseline characteristics

Reporting groups	
Reporting group title	IV NEPA FDC
Reporting group description:	
IV fosnetupitant/palonosetron (260 mg/0.25 mg) FDC (IV NEPA FDC) was to be administered as a 30-min infusion of a 50-mL solution on Day 1 of each cycle. The 30-min (±5 min) IV NEPA FDC infusion was to be started 30 min prior to the start of the reference chemotherapy administration. The 30-min IV infusion was to be completed before starting chemotherapy administration.	
Reporting group title	Oral NEPA FDC
Reporting group description:	
Oral netupitant/palonosetron (300 mg/0.50 mg) FDC (Oral NEPA FDC) was to be administered on Day 1 of each cycle. Oral NEPA FDC capsule was to be administered 60 min prior to the start of the reference chemotherapy administration.	

Reporting group values	IV NEPA FDC	Oral NEPA FDC	Total
Number of subjects	203	202	405
Age categorical Units: Subjects			
Adults (18-64 years)	129	133	262
From 65-84 years	74	69	143
Age continuous Units: years			
arithmetic mean	60	58.9	
standard deviation	± 9.7	± 10.6	-
Gender categorical Units: Subjects			
Female	96	94	190
Male	107	108	215

End points

End points reporting groups

Reporting group title	IV NEPA FDC

Reporting group description:

IV fosnetupitant/palonosetron (260 mg/0.25 mg) FDC (IV NEPA FDC) was to be administered as a 30-min infusion of a 50-mL solution on Day 1 of each cycle. The 30-min (±5 min) IV NEPA FDC infusion was to be started 30 min prior to the start of the reference chemotherapy administration. The 30-min IV infusion was to be completed before starting chemotherapy administration.

Reporting group title	Oral NEPA FDC

Reporting group description:

Oral netupitant/palonosetron (300 mg/0.50 mg) FDC (Oral NEPA FDC) was to be administered on Day 1 of each cycle. Oral NEPA FDC capsule was to be administered 60 min prior to the start of the reference chemotherapy administration.

Subject analysis set title	Full Analysis Set: IV NEPA FDC
Subject analysis set type	Full analysis

Subject analysis set description:

Included all randomized patients who received the HEC regimen and active study drug (including partial infusion). Following the intent-to-treat principle, patients were assigned to the treatment group to which they were randomized.

Subject analysis set title	Safety population: IV NEPA FDC
Subject analysis set type	Safety analysis

Subject analysis set description:

Included all patients who received at least one dose of active study drug (including partial infusion). Patients were assigned to treatment groups according to the actual treatment received.

Subject analysis set title	Full Analysis Set: Oral NEPA FDC
Subject analysis set type	Full analysis

Subject analysis set description:

Included all randomized patients who received the HEC regimen and active study drug (including partial infusion). Following the intent-to-treat principle, patients were assigned to the treatment group to which they were randomized.

Subject analysis set title	Safety Population: Oral NEPA FDC
Subject analysis set type	Safety analysis

Subject analysis set description:

Included all patients who received at least one dose of active study drug (including partial infusion). Patients were assigned to treatment groups according to the actual treatment received.

Primary: Complete Response in acute phase: Cycle 1

End point title	Complete Response in acute phase: Cycle 1

End point description:

Complete response in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-24 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Primary

End point timeframe:

Acute phase (0-24 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	203	201		
Units: Proportion				
number (confidence interval 95%)	92.6 (88.2 to 95.5)	90.5 (85.7 to 93.9)		

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: Oral NEPA FDC v Full Analysis Set: IV NEPA FDC
Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	other[1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	7.2

Notes:

[1] - No formal test was planned for this endpoint.

Primary: Complete Response in delayed phase: Cycle 1

End point title	Complete Response in delayed phase: Cycle 1

End point description:

Complete response in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting >24-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Primary

End point timeframe:

Delayed phase (>24-120 h)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	203	201		
Units: Proportion				
number (confidence interval 95%)	78.3 (72.2 to 83.4)	87.6 (82.3 to 91.4)		

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	other[2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.8
upper limit	-2.2

Notes:

[2] - No formal test was planned for this endpoint.

Primary: Complete Response in overall phase: Cycle 1

End point title	Complete Response in overall phase: Cycle 1

End point description:

Complete response in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Primary

End point timeframe:

Overall phase (0-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	203	201		
Units: Proportion				
number (confidence interval 95%)	76.8 (70.6 to 82.1)	84.1 (78.4 to 88.5)		

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	other[3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-7.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.2
upper limit	-0.1

Notes:

[3] - No formal test was planned for this endpoint.

Secondary: Complete Response in acute phase: Cycle 2

End point title	Complete Response in acute phase: Cycle 2

End point description:

Complete response in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-24 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Acute phase (0-24 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179[4]	176[5]		
Units: Proportion				
number (confidence interval 95%)	89.9 (84.7 to 93.5)	90.3 (85.1 to 93.9)		

Notes:

[4] - Discontinuation after cycle 1

[5] - Discontinuation after cycle 1

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC

Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	other[6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	6.3

Notes:

[6] - No formal test was planned for this endpoint.

Secondary: Complete Response in delayed phase: Cycle 2

End point title	Complete Response in delayed phase: Cycle 2

End point description:

Complete response in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting >24-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Delayed phase (>24-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179[7]	176[8]		
Units: Proportion				
number (confidence interval 95%)	82.1 (75.9 to 87)	89.2 (83.8 to 93)		

Notes:

[7] - Discontinuation after cycle 1

[8] - Discontinuation after cycle 1

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	other[9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-6.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.1
upper limit	0.4

Notes:

[9] - No formal test was planned for this endpoint.

Secondary: Complete Response in overall phase: Cycle 2

End point title	Complete Response in overall phase: Cycle 2

End point description:

Complete response in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Overall phase (0-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179[10]	176[11]		
Units: Proportion				
number (confidence interval 95%)	79.9 (73.4 to 85.1)	85.8 (79.9 to 90.2)		

Notes:

[10] - Discontinuation after cycle 1

[11] - Discontinuation after cycle 1

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	other[12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.7
upper limit	2

Notes:

[12] - No formal test was planned for this endpoint.

Secondary: Complete Response in acute phase: Cycle 3

End point title	Complete Response in acute phase: Cycle 3

End point description:

Complete response in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-24 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Acute phase (0-24 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163[13]	150[14]		
Units: Proportion				
number (confidence interval 95%)	92.6 (87.6 to 95.7)	96 (91.5 to 98.2)		

Notes:

[13] - Discontinuation after previous cycle

[14] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	other[15]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	2.4

Notes:

[15] - No formal test was planned for this endpoint.

Secondary: Complete Response in delayed phase: Cycle 3

End point title	Complete Response in delayed phase: Cycle 3

End point description:

Complete response in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting >24-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Delayed phase (>24-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163[16]	150[17]		
Units: Proportion				
number (confidence interval 95%)	85.9 (79.7 to 90.4)	90 (84.2 to 93.8)		

Notes:

[16] - Discontinuation after previous cycle

[17] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	other[18]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	4

Notes:

[18] - No formal test was planned for this endpoint.

Secondary: Complete Response in overall phase: Cycle 3

End point title	Complete Response in overall phase: Cycle 3

End point description:

Complete response in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Overall phase (0-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163[19]	150[20]		
Units: Proportion				
number (confidence interval 95%)	84 (77.7 to 88.9)	88.7 (82.6 to 92.8)		

Notes:

[19] - Discontinuation after previous cycle

[20] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	other[21]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.1
upper limit	4.2

Notes:

[21] - No formal test was planned for this endpoint.

Secondary: Complete Response in acute phase: Cycle 4

End point title	Complete Response in acute phase: Cycle 4

End point description:

Complete response in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-24 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Acute phase (0-24 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122[22]	117[23]		
Units: Proportion				
number (confidence interval 95%)	90.2 (83.6 to 94.3)	99.1 (95.3 to 99.8)		

Notes:

[22] - Discontinuation after previous cycle

[23] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other[24]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.9
upper limit	-2.2

Notes:

[24] - No formal test was planned for this endpoint.

Secondary: Complete Response in delayed phase: Cycle 4

End point title	Complete Response in delayed phase: Cycle 4

End point description:

Complete response in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting >24-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Delayed phase (>24-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122[25]	117[26]		
Units: Proportion				
number (confidence interval 95%)	86.1 (78.8 to 91.1)	98.3 (94 to 99.5)		

Notes:

[25] - Discontinuation after previous cycle

[26] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other[27]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-9.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.4
upper limit	-3.8

Notes:

[27] - No formal test was planned for this endpoint.

Secondary: Complete Response in overall phase: Cycle 4

End point title	Complete Response in overall phase: Cycle 4

End point description:

Complete response in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Overall phase (0-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122[28]	117[29]		
Units: Proportion				
number (confidence interval 95%)	83.6 (76 to 89.1)	97.4 (92.7 to 99.1)		

Notes:

[28] - Discontinuation after previous cycle

[29] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other[30]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-11.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.6
upper limit	-4.6

Notes:

[30] - No formal test was planned for this endpoint.

Secondary: Absence of Emetic Episodes in acute phase: Cycle 1

End point title	Absence of Emetic Episodes in acute phase: Cycle 1

End point description:

Absence of Emetic Episodes in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-24 hour after start of reference highly emetogenic chemotherapy [HEC].
Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Acute phase (0-24 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	203	201		
Units: Proportion				
number (confidence interval 95%)	95.1 (91.2 to 97.3)	93 (88.6 to 95.8)		

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC

Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	other[31]
Parameter estimate	Risk difference (RD)
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	6.5

Notes:

[31] - No formal test was planned for this endpoint.

Secondary: Absence of Emetic Episodes in delayed phase: Cycle 1

End point title	Absence of Emetic Episodes in delayed phase: Cycle 1

End point description:

Absence of Emetic Episodes in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting >24-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Delayed phase (>24-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	203	201		
Units: Proportion				
number (confidence interval 95%)	85.2 (79.7 to 89.4)	91.5 (86.9 to 94.7)		

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	other[32]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-6.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	-0.4

Notes:

[32] - No formal test was planned for this endpoint.

Secondary: Absence of Emetic Episodes in overall phase: Cycle 1

End point title	Absence of Emetic Episodes in overall phase: Cycle 1

End point description:

Absence of Emetic Episodes in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Overall phase (0-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	203	201		
Units: Proportion				
number (confidence interval 95%)	84.2 (78.6 to 88.6)	88.6 (83.4 to 92.3)		

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	other[33]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.4
upper limit	1.8

Notes:

[33] - No formal test was planned for this endpoint.

Secondary: Absence of Emetic Episodes in acute phase: Cycle 2

End point title	Absence of Emetic Episodes in acute phase: Cycle 2

End point description:

Absence of Emetic Episodes in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-24 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Acute phase (0-24 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179[34]	176[35]		
Units: Proportion				
number (confidence interval 95%)	91.6 (86.6 to 94.9)	93.8 (89.2 to 96.5)		

Notes:

[34] - Discontinuation after cycle 1

[35] - Discontinuation after cycle 1

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	other[36]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	3.2

Notes:

[36] - No formal test was planned for this endpoint.

Secondary: Absence of Emetic Episodes in delayed phase: Cycle 2

End point title	Absence of Emetic Episodes in delayed phase: Cycle 2

End point description:

Absence of Emetic Episodes in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting >24-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Delayed phase (>24-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179[37]	176[38]		
Units: Proportion				
number (confidence interval 95%)	87.2 (81.5 to 91.3)	94.9 (90.6 to 97.3)		

Notes:

[37] - Discontinuation after cycle 1

[38] - Discontinuation after cycle 1

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	other[39]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.2
upper limit	-2

Notes:

[39] - No formal test was planned for this endpoint.

Secondary: Absence of Emetic Episodes in overall phase: Cycle 2

End point title	Absence of Emetic Episodes in overall phase: Cycle 2

End point description:

Absence of Emetic Episodes in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Overall phase (0-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179[40]	176[41]		
Units: Proportion				
number (confidence interval 95%)	85.5 (79.6 to 89.9)	93.2 (88.5 to 96.1)		

Notes:

[40] - Discontinuation after cycle 1

[41] - Discontinuation after cycle 1

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	other[42]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.8
upper limit	-1.7

Notes:

[42] - No formal test was planned for this endpoint.

Secondary: Absence of Emetic Episodes in acute phase: Cycle 3

End point title	Absence of Emetic Episodes in acute phase: Cycle 3

End point description:

Absence of Emetic Episodes in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-24 hour after start of reference highly emetogenic chemotherapy [HEC].
Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Acute phase (0-24 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163[43]	150[44]		
Units: Proportion				
number (confidence interval 95%)	94.5 (89.8 to 97.1)	96.7 (92.4 to 98.6)		

Notes:

[43] - Discontinuation after previous cycle

[44] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	other[45]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	3

Notes:

[45] - No formal test was planned for this endpoint.

Secondary: Absence of Emetic Episodes in delayed phase: Cycle 3

End point title	Absence of Emetic Episodes in delayed phase: Cycle 3

End point description:

Absence of Emetic Episodes in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting >24-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Delayed phase (>24-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163[46]	150[47]		
Units: Proportion				
number (confidence interval 95%)	92 (86.8 to 95.3)	93.3 (88.2 to 96.3)		

Notes:

[46] - Discontinuation after previous cycle

[47] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	other[48]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	4.8

Notes:

[48] - No formal test was planned for this endpoint.

Secondary: Absence of Emetic Episodes in overall phase: Cycle 3

End point title	Absence of Emetic Episodes in overall phase: Cycle 3

End point description:

Absence of Emetic Episodes in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Overall phase (0-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163[49]	150[50]		
Units: Proportion				
number (confidence interval 95%)	90.2 (84.7 to 93.9)	92.7 (87.3 to 95.9)		

Notes:

[49] - Discontinuation after previous cycle

[50] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	other[51]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	4.4

Notes:

[51] - No formal test was planned for this endpoint.

Secondary: Absence of Emetic Episodes in acute phase: Cycle 4

End point title	Absence of Emetic Episodes in acute phase: Cycle 4

End point description:

Absence of Emetic Episodes in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-24 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Acute phase (0-24 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122[52]	117[53]		
Units: Proportion				
number (confidence interval 95%)	92.6 (86.6 to 96.1)	100 (96.8 to 100)		

Notes:

[52] - Discontinuation after previous cycle

[53] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC

Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other[54]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	-2.3

Notes:

[54] - No formal test was planned for this endpoint.

Secondary: Absence of Emetic Episodes in delayed phase: Cycle 4

End point title	Absence of Emetic Episodes in delayed phase: Cycle 4

End point description:

Absence of Emetic Episodes in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting >24-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Delayed phase (>24-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122[55]	117[56]		
Units: Proportion				
number (confidence interval 95%)	90.2 (83.6 to 94.3)	99.1 (95.3 to 99.8)		

Notes:

[55] - Discontinuation after previous cycle

[56] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other[57]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-7.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.7
upper limit	-2.4

Notes:

[57] - No formal test was planned for this endpoint.

Secondary: Absence of Emetic Episodes in overall phase: Cycle 4

End point title	Absence of Emetic Episodes in overall phase: Cycle 4

End point description:

Absence of Emetic Episodes in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Overall phase (0-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122[58]	117[59]		
Units: Proportion				
number (confidence interval 95%)	88.5 (81.7 to 93)	99.1 (95.3 to 99.8)		

Notes:

[58] - Discontinuation after previous cycle

[59] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other[60]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-9.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.7
upper limit	-3.7

Notes:

[60] - No formal test was planned for this endpoint.

Secondary: Absence of Rescue Medication in acute phase: Cycle 1

End point title	Absence of Rescue Medication in acute phase: Cycle 1

End point description:

Absence of Rescue Medication in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-24 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Acute phase (0-24 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	203	201		
Units: Proportion				
number (confidence interval 95%)	96.1 (92.4 to 98)	93 (88.6 to 95.8)		

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	other[61]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	7.3

Notes:

[61] - No formal test was planned for this endpoint.

Secondary: Absence of Rescue Medication in delayed phase: Cycle 1

End point title	Absence of Rescue Medication in delayed phase: Cycle 1

End point description:

Absence of Rescue Medication in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting >24-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Delayed phase (>24-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	203	201		
Units: Proportion				
number (confidence interval 95%)	84.7 (79.1 to 89)	91.5 (86.9 to 94.7)		

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	other[62]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-6.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.9
upper limit	-1

Notes:

[62] - No formal test was planned for this endpoint.

Secondary: Absence of Rescue Medication in overall phase: Cycle 1

End point title	Absence of Rescue Medication in overall phase: Cycle 1

End point description:

Absence of Rescue Medication in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Overall phase (0-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	203	201		
Units: Proportion				
number (confidence interval 95%)	82.8 (77 to 87.3)	89.1 (84 to 92.7)		

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)
Statistical analysis description:	
The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.	
Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	other[63]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.3
upper limit	0.2

Notes:

[63] - No formal test was planned for this endpoint.

Secondary: Absence of Rescue Medication in acute phase: Cycle 2

End point title	Absence of Rescue Medication in acute phase: Cycle 2
End point description:	
Absence of Rescue Medication in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-24 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.	
End point type	Secondary
End point timeframe:	
Acute phase (0-24 hour)	

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179[64]	176[65]		
Units: Proportion				
number (confidence interval 95%)	94.4 (90 to 96.9)	91.5 (86.4 to 94.8)		

Notes:

[64] - Discontinuation after cycle 1

[65] - Discontinuation after cycle 1

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	other[66]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	8.9

Notes:

[66] - No formal test was planned for this endpoint.

Secondary: Absence of Rescue Medication in delayed phase: Cycle 2

End point title	Absence of Rescue Medication in delayed phase: Cycle 2

End point description:

Absence of Rescue Medication in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting >24-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Delayed phase (>24-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179[67]	176[68]		
Units: Proportion				
number (confidence interval 95%)	87.2 (81.5 to 91.3)	89.8 (84.4 to 93.4)		

Notes:

[67] - Discontinuation after cycle 1

[68] - Discontinuation after cycle 1

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	other[69]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	4

Notes:

[69] - No formal test was planned for this endpoint.

Secondary: Absence of Rescue Medication in overall phase: Cycle 2

End point title	Absence of Rescue Medication in overall phase: Cycle 2

End point description:

Absence of Rescue Medication in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Overall phase (0-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179[70]	176[71]		
Units: Proportion				
number (confidence interval 95%)	85.5 (79.6 to 89.9)	86.9 (81.2 to 91.1)		

Notes:

[70] - Discontinuation after cycle

[71] - Discontinuation after cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	other[72]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.4
upper limit	6.1

Notes:

[72] - No formal test was planned for this endpoint.

Secondary: Absence of Rescue Medication in acute phase: Cycle 3

End point title	Absence of Rescue Medication in acute phase: Cycle 3

End point description:

Absence of Rescue Medication in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-24 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Acute phase (0-24 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163[73]	150[74]		
Units: Proportion				
number (confidence interval 95%)	95.7 (91.4 to 97.9)	96.7 (92.4 to 98.6)		

Notes:

[73] - Discontinuation after previous cycle

[74] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC

Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	other[75]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	3.5

Notes:

[75] - No formal test was planned for this endpoint.

Secondary: Absence of Rescue Medication in delayed phase: Cycle 3

End point title	Absence of Rescue Medication in delayed phase: Cycle 3

End point description:

Absence of Rescue Medication in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting >24-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Delayed phase (>24-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163[76]	150[77]		
Units: Proportion				
number (confidence interval 95%)	90.8 (85.4 to 94.3)	90.7 (84.9 to 94.4)		

Notes:

[76] - Discontinuation after previous cycle

[77] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	other[78]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	1.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	6.9

Notes:

[78] - No formal test was planned for this endpoint.

Secondary: Absence of Rescue Medication in overall phase: Cycle 3

End point title	Absence of Rescue Medication in overall phase: Cycle 3

End point description:

Absence of Rescue Medication in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Overall phase (0-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163[79]	150[80]		
Units: Proportion				
number (confidence interval 95%)	89.6 (83.9 to 93.4)	90 (84.2 to 93.8)		

Notes:

[79] - Discontinuation after previous cycle

[80] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	other[81]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	6.9

Notes:

[81] - No formal test was planned for this endpoint.

Secondary: Absence of Rescue Medication in acute phase: Cycle 4

End point title	Absence of Rescue Medication in acute phase: Cycle 4

End point description:

Absence of Rescue Medication in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-24 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Acute phase (0-24 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122[82]	117[83]		
Units: Proportion				
number (confidence interval 95%)	93.4 (87.6 to 96.6)	99.1 (95.3 to 99.8)		

Notes:

[82] - Discontinuation after previous cycle

[83] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other[84]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.6
upper limit	-0.4

Notes:

[84] - No formal test was planned for this endpoint.

Secondary: Absence of Rescue Medication in delayed phase: Cycle 4

End point title	Absence of Rescue Medication in delayed phase: Cycle 4

End point description:

Absence of Rescue Medication in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting >24-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Delayed phase (>24-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122[85]	117[86]		
Units: Proportion				
number (confidence interval 95%)	90.2 (83.6 to 94.3)	98.3 (94 to 99.5)		

Notes:

[85] - Discontinuation after previous cycle

[86] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other[87]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	-1.1

Notes:

[87] - No formal test was planned for this endpoint.

Secondary: Absence of Rescue Medication in overall phase: Cycle 4

End point title	Absence of Rescue Medication in overall phase: Cycle 4

End point description:

Absence of Rescue Medication in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Overall phase (0-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122[88]	117[89]		
Units: Proportion				
number (confidence interval 95%)	88.5 (81.7 to 93)	97.4 (92.7 to 99.1)		

Notes:

[88] - Discontinuation after previous cycle

[89] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other[90]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.3
upper limit	-1.1

Notes:

[90] - No formal test was planned for this endpoint.

Secondary: Absence of Significant Nausea in acute phase: Cycle 1

End point title	Absence of Significant Nausea in acute phase: Cycle 1

End point description:

Absence of Significant Nausea in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-24 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Acute phase (0-24 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	203	201		
Units: Proportion				
number (confidence interval 95%)	90.1 (85.3 to 93.5)	93 (88.6 to 95.8)		

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	other[91]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	2.3

Notes:

[91] - No formal test was planned for this endpoint.

Secondary: Absence of Significant Nausea in delayed phase: Cycle 1

End point title	Absence of Significant Nausea in delayed phase: Cycle 1

End point description:

Absence of Significant Nausea in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting >24-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Delayed phase (>24-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	203	201		
Units: Proportion				
number (confidence interval 95%)	81.3 (75.4 to 86)	89.1 (84 to 92.7)		

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	other[92]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.7
upper limit	-0.8

Notes:

[92] - No formal test was planned for this endpoint.

Secondary: Absence of Significant Nausea in overall phase: Cycle 1

End point title	Absence of Significant Nausea in overall phase: Cycle 1

End point description:

Absence of Significant Nausea in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Overall phase (0-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	203	201		
Units: Proportion				
number (confidence interval 95%)	79.3 (73.2 to 84.3)	86.6 (81.2 to 90.6)		

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	other[93]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.8
upper limit	-0.2

Notes:

[93] - No formal test was planned for this endpoint.

Secondary: Absence of Significant Nausea in acute phase: Cycle 2

End point title	Absence of Significant Nausea in acute phase: Cycle 2

End point description:

Absence of Significant Nausea in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-24 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Acute phase (0-24 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179[94]	176[95]		
Units: Proportion				
number (confidence interval 95%)	91.1 (86 to 94.4)	93.8 (89.2 to 96.5)		

Notes:

[94] - Discontinuation after cycle 1

[95] - Discontinuation after cycle 1

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC

Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	other[96]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	3.4

Notes:

[96] - No formal test was planned for this endpoint.

Secondary: Absence of Significant Nausea in delayed phase: Cycle 2

End point title	Absence of Significant Nausea in delayed phase: Cycle 2

End point description:

Absence of Significant Nausea in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting >24-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Delayed phase (>24-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179[97]	176[98]		
Units: Proportion				
number (confidence interval 95%)	81 (74.6 to 86.1)	89.2 (83.8 to 93)		

Notes:

[97] - Discontinuation after cycle 1

[98] - Discontinuation after cycle 1

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	other[99]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-8.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.1
upper limit	-1.7

Notes:

[99] - No formal test was planned for this endpoint.

Secondary: Absence of Significant Nausea in overall phase: Cycle 2

End point title	Absence of Significant Nausea in overall phase: Cycle 2

End point description:

Absence of Significant Nausea in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Overall phase (0-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179[100]	176[101]		
Units: Proportion				
number (confidence interval 95%)	79.9 (73.4 to 85.1)	86.9 (81.2 to 91.1)		

Notes:

[100] - Discontinuation after cycle 1

[101] - Discontinuation after cycle 1

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	other[102]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.4
upper limit	-0.3

Notes:

[102] - No formal test was planned for this endpoint.

Secondary: Absence of Significant Nausea in acute phase: Cycle 3

End point title	Absence of Significant Nausea in acute phase: Cycle 3

End point description:

Absence of Significant Nausea in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-24 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Acute phase (0-24 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163[103]	150[104]		
Units: Proportion				
number (confidence interval 95%)	92.6 (87.6 to 95.7)	95.3 (90.7 to 97.7)		

Notes:

[103] - Discontinuation after previous cycle

[104] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	other[105]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	3.2

Notes:

[105] - No formal test was planned for this endpoint.

Secondary: Absence of Significant Nausea in delayed phase: Cycle 3

End point title	Absence of Significant Nausea in delayed phase: Cycle 3

End point description:

Absence of Significant Nausea in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting >24-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Delayed phase (>24-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163[106]	150[107]		
Units: Proportion				
number (confidence interval 95%)	86.5 (80.4 to 90.9)	90 (84.2 to 93.8)		

Notes:

[106] - Discontinuation after previous cycle

[107] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	other[108]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	4.2

Notes:

[108] - No formal test was planned for this endpoint.

Secondary: Absence of Significant Nausea in overall phase: Cycle 3

End point title	Absence of Significant Nausea in overall phase: Cycle 3

End point description:

Absence of Significant Nausea in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Overall phase (0-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163[109]	150[110]		
Units: Proportion				
number (confidence interval 95%)	84 (77.7 to 88.9)	90 (84.2 to 93.8)		

Notes:

[109] - Discontinuation after previous cycle

[110] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	other[111]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	2.3

Notes:

[111] - No formal test was planned for this endpoint.

Secondary: Absence of Significant Nausea in acute phase: Cycle 4

End point title	Absence of Significant Nausea in acute phase: Cycle 4

End point description:

Absence of Significant Nausea in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-24 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Acute phase (0-24 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122[112]	117[113]		
Units: Proportion				
number (confidence interval 95%)	90.2 (83.6 to 94.3)	94.9 (89.3 to 97.6)		

Notes:

[112] - Discontinuation after previous cycle

[113] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other[114]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	3.3

Notes:

[114] - No formal test was planned for this endpoint.

Secondary: Absence of Significant Nausea in delayed phase: Cycle 4

End point title	Absence of Significant Nausea in delayed phase: Cycle 4

End point description:

Absence of Significant Nausea in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting >24-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Delayed phase (>24-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122[115]	117[116]		
Units: Proportion				
number (confidence interval 95%)	87.7 (80.7 to 92.4)	94.9 (89.3 to 97.6)		

Notes:

[115] - Discontinuation after previous cycle

[116] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other[117]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.5
upper limit	1.1

Notes:

[117] - No formal test was planned for this endpoint.

Secondary: Absence of Significant Nausea in overall phase: Cycle 4

End point title	Absence of Significant Nausea in overall phase: Cycle 4

End point description:

Absence of Significant Nausea in the acute phase which is defined as the absence of chemotherapy induced nausea or vomiting 0-120 hour after start of reference highly emetogenic chemotherapy [HEC]. Confidence interval of proportions are obtained by using the Newcombe-Wilson method.

End point type	Secondary

End point timeframe:

Overall phase (0-120 hour)

End point values	Full Analysis Set: IV NEPA FDC	Full Analysis Set: Oral NEPA FDC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122[118]	117[119]		
Units: Proportion				
number (confidence interval 95%)	84.4 (77 to 89.8)	94 (88.2 to 97.1)		

Notes:

[118] - Discontinuation after previous cycle

[119] - Discontinuation after previous cycle

Statistical analyses

Statistical analysis title	Statistical analysis (FAS)

Statistical analysis description:

The Cochran-Mantel-Haenszel test stratified by gender and country was used to compare both treatment with a 2-sided 95% confidence interval.

Comparison groups	Full Analysis Set: IV NEPA FDC v Full Analysis Set: Oral NEPA FDC
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other[120]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14
upper limit	0.1

Notes:

[120] - No formal test was planned for this endpoint.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from Informed consent signature or day 1 of each cycle up to the follow-up visit contact which is a maximum of 35 days for each cycle. The study contains four (4) cycles with a 21 day interval between consecutive cycles.

Adverse event reporting additional description:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship wit h this treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Oral NEPA FDC

Reporting group description:

Oral netupitant/palonosetron (300 mg/0.50 mg) FDC (Oral NEPA FDC) was to be administered on Day 1 of each cycle. Oral NEPA FDC capsule was to be administered 60 min prior to the start of the reference chemotherapy administration.

Reporting group title	IV NEPA FDC

Reporting group description:

IV fosnetupitant/palonosetron (260 mg/0.25 mg) FDC (IV NEPA FDC) was to be administered as a 30-min infusion of a 50-mL solution on Day 1 of each cycle. The 30-min (±5 min) IV NEPA FDC infusion was to be started 30 min prior to the start of the reference chemotherapy administration. The 30-min IV infusion was to be completed before starting chemotherapy administration.

Serious adverse events	Oral NEPA FDC	IV NEPA FDC	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 201 (0.00%)	0 / 203 (0.00%)	
number of deaths (all causes)	14	10	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Oral NEPA FDC	IV NEPA FDC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	170 / 201 (84.58%)	161 / 203 (79.31%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	24 / 201 (11.94%)	15 / 203 (7.39%)	
occurrences (all)	43	25	

Aspartate aminotransferase increased			
subjects affected / exposed	19 / 201 (9.45%)	12 / 203 (5.91%)	
occurrences (all)	30	17	
Blood creatinine increased			
subjects affected / exposed	6 / 201 (2.99%)	11 / 203 (5.42%)	
occurrences (all)	10	15	
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 201 (6.47%)	8 / 203 (3.94%)	
occurrences (all)	16	12	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 201 (4.48%)	11 / 203 (5.42%)	
occurrences (all)	21	19	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	34 / 201 (16.92%)	33 / 203 (16.26%)	
occurrences (all)	52	54	
Leukopenia			
subjects affected / exposed	21 / 201 (10.45%)	21 / 203 (10.34%)	
occurrences (all)	35	28	
Neutropenia			
subjects affected / exposed	52 / 201 (25.87%)	57 / 203 (28.08%)	
occurrences (all)	81	89	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	17 / 201 (8.46%)	13 / 203 (6.40%)	
occurrences (all)	26	16	
Fatigue			
subjects affected / exposed	17 / 201 (8.46%)	17 / 203 (8.37%)	
occurrences (all)	32	30	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	26 / 201 (12.94%)	21 / 203 (10.34%)	
occurrences (all)	30	29	
Nausea			

subjects affected / exposed occurrences (all)	14 / 201 (6.97%) 20	20 / 203 (9.85%) 28	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	 29 / 201 (14.43%) 31	 32 / 203 (15.76%) 35	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 11 / 201 (5.47%) 14	 7 / 203 (3.45%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 July 2015	The following change to the study protocol is implemented to comply with a request from the US Food and Drug Administration: - During the conduct of the study, a Data Safety Monitoring Board (DSMB) will periodically review safety data.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported