Clinical trial results:
A standard regimen of dexamethasone in comparison to two dex-sparing regimens in addition to NEPA in preventing CINV in naïve NSCLC patients to be treated with cisplatin based chemotherapy: a three-arm, open-label, randomized study

Summary

EudraCT number	2015-005704-29
Trial protocol	IT
Global end of trial date	16 December 2019

Results information

Result version number	v1 (current)
This version publication date	26 June 2022
First version publication date	26 June 2022

Trial information

Trial identification

Sponsor protocol code	LUNG-NEPA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04201769
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Consorzio Oncotech
Sponsor organisation address	Via Sergio Pansini, 5, Naples, Italy, 80131
Public contact	Clinical Operations, Clinical Research Technology, +39 089301545, lunepa@oncotech.org
Scientific contact	Clinical Operations, Clinical Research Technology, +39 089301545, lunepa@oncotech.org

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	08 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 December 2019
Global end of trial reached?	Yes
Global end of trial date	16 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the possibility to reduce the overall exposure to dexamethasone (DEX), when administered with an oral fixed-dose combination of netupitant and palonosetron (NEPA), to prevent chemotherapy-induced nausea and vomiting in non-small cell lung cancer (NSCLC) patients receiving a cisplatin-based chemotherapy

Protection of trial subjects:

For women of childbearing potential age: reliable contraceptive measures had to be used during all the planned course of chemotherapy and up to 30 days after last NEPA administration.

All patients were allowed to take rescue medication throughout the study period for nausea or vomiting, if necessary. The choice of recommended rescue medicine was either DEX or metoclopramide and was at the discretion of each investigator.

No other specific measures to protect trial subjects were required by the study participation.

Background therapy:

Cisplatin-based chemotherapy (cisplatin dose ≥70 mg/m2)

Evidence for comparator: -

Actual start date of recruitment	25 November 2016
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	Italy: 252
Worldwide total number of subjects	252
EEA total number of subjects	252

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)	127
From 65 to 84 years	125
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment process for the trial has been conducted from November 2016 to November 2019 in 24 Italian centers.
All patients included in this study provided a written informed consent.

Pre-assignment

Screening details:

Age ≥ 18 years; confirmed diagnosis of NSCLC, chemotherapy-naïve, scheduled to receive the first course of cisplatin (≥70 mg/m2)-based chemotherapy (cisplatin either alone or in combination with antineoplastic agents with low or minimal emetogenic potential), ECOG Performance Status = 0-1; adequate hematologic, hepatic, and renal functions.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A (or DEX1 arm)

Arm description:

Treatment arm A: On day 1 oral NEPA and intravenous dexamethasone 12 mg.
No further anti-emetic prophylaxis on days 2 thorough 4.

Arm type	Experimental
Investigational medicinal product name	Akynzeo
Investigational medicinal product code	IMP 1
Other name	Netupitant/palonosetron, NEPA
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients in each arm received oral NEPA (a capsule containing netupitant 300 mg/palonosetron 0.50 mg) 1 hour before the administration of cisplatin on the first day of chemotherapy (day 1).

Investigational medicinal product name	Desametasone
Investigational medicinal product code	IMP 2
Other name	Dexamethasone, DEX
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients in each arm received DEX 12 mg intravenously a maximum of 30 minutes before the administration of cisplatin on day 1.

Arm title	Arm B (or DEX3 arm)

Arm description:

Treatment arm B: On day 1 oral NEPA and intravenous dexamethasone 12 mg.
Oral dexamethasone 4 mg once per day in the morning of days 2 and 3.

Arm type	Experimental
Investigational medicinal product name	Akynzeo
Investigational medicinal product code	IMP 1
Other name	Netupitant/palonosetron, NEPA
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients in each arm received oral NEPA (a capsule containing netupitant 300 mg/palonosetron 0.50 mg) 1 hour before the administration of cisplatin on the first day of chemotherapy (day 1).

Investigational medicinal product name	Desametasone
Investigational medicinal product code	IMP 2
Other name	Dexamethasone, DEX
Pharmaceutical forms	Oral drops, Solution for injection
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Patients in each arm received DEX 12 mg intravenously a maximum of 30 minutes before the administration of cisplatin on day 1.
In the DEX3 arm, patients received oral DEX 4 mg once per day in the morning of days 2 and 3.

Arm title	Arm C (or DEX4 arm)

Arm description:

Treatment arm C: On day 1 oral NEPA and intravenous dexamethasone 12 mg.
Oral dexamethasone 4 mg twice per day on days 2 thorough 4.

Arm type	Active comparator
Investigational medicinal product name	Akynzeo
Investigational medicinal product code	IMP 1
Other name	Netupitant/palonosetron, NEPA
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients in each arm received oral NEPA (a capsule containing netupitant 300 mg/palonosetron 0.50 mg) 1 hour before the administration of cisplatin on the first day of chemotherapy (day 1).

Investigational medicinal product name	Desametasone
Investigational medicinal product code	IMP 2
Other name	Dexamethasone, DEX
Pharmaceutical forms	Oral drops, Solution for injection
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Patients in each arm received DEX 12 mg intravenously a maximum of 30 minutes before the administration of cisplatin on day 1.
In the DEX4 arm, patients received oral DEX 4 mg twice per day on days 2 thorough 4.

Number of subjects in period 1	Arm A (or DEX1 arm)	Arm B (or DEX3 arm)	Arm C (or DEX4 arm)
Started	84	85	83
Completed	75	75	76
Not completed	9	10	7
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	1	-	-
Not treated with IMP due to QuantiFERON test value	-	1	-
Adverse event, non-fatal	1	-	1
Death	3	1	1
Not Compliance	1	1	1
Unknown	2	4	3

Patient changed chemotherapy scheme	-	1	-
Hospitalization due to Progressive Disease	-	1	-
Lost to follow-up	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm A (or DEX1 arm)
Reporting group description:	
Treatment arm A: On day 1 oral NEPA and intravenous dexamethasone 12 mg. No further anti-emetic prophylaxis on days 2 thorough 4.	
Reporting group title	Arm B (or DEX3 arm)
Reporting group description:	
Treatment arm B: On day 1 oral NEPA and intravenous dexamethasone 12 mg. Oral dexamethasone 4 mg once per day in the morning of days 2 and 3.	
Reporting group title	Arm C (or DEX4 arm)
Reporting group description:	
Treatment arm C: On day 1 oral NEPA and intravenous dexamethasone 12 mg. Oral dexamethasone 4 mg twice per day on days 2 thorough 4.	

Reporting group values	Arm A (or DEX1 arm)	Arm B (or DEX3 arm)	Arm C (or DEX4 arm)
Number of subjects	84	85	83
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Demographic characteristics for the Intention To Treat set appear consistent to those of the standard reference population (namely the target population to which the study therapies are addressed) and homogeneous across the three randomized arms.			
Units: years			
arithmetic mean	63.94	62.72	63.28
standard deviation	± 7.16	± 7.98	± 8.17
Gender categorical Units: Subjects			
Female	24	34	25
Male	60	51	58
ECOG Performance Status			
Patients were required to have an Eastern Cooperative Oncology Group Performance Status of 0 or 1 (0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work)			
Units: Subjects			
0 - Fully active, able to carry on...	66	70	62
1 - Restricted in physically strenuous activity...	18	15	21
Cisplatin Dose categorical			

In this study, chemotherapy-naïve patients received high-dose cisplatin (≥70 mg/m2) either alone or in combination with antineoplastic agents with low or minimal emetogenic potential. Only one patient (in the Arm C) received cisplatin dose <70 mg/m2.			
Units: Subjects			
Dose = 70 mg/m2	20	21	22
Dose >70 mg/m2	64	64	61
Concomitant Chemotherapy			
Eligible patients were chemotherapy-naïve and scheduled to receive the first course of cisplatin (≥70 mg/m2)-based chemotherapy. Patients could receive cisplatin either alone or in combination with antineoplastic agents with low or minimal emetogenic potential.			
Units: Subjects			
Pemetrexed	37	42	44
Gemcitabine	22	21	22
Vinorelbine	21	18	14
Other	4	4	3
BMI			
Body Mass Index			
Units: kilogram(s)/square metre			
arithmetic mean	24.72	24.59	25
standard deviation	± 4.22	± 4.15	± 4.03
Cisplatin Dose Units: milligram(s)/square metre			
arithmetic mean	75.04	75.27	74.28
standard deviation	± 4.22	± 4.42	± 5.89

Reporting group values	Total		
Number of subjects	252		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Demographic characteristics for the Intention To Treat set appear consistent to those of the standard reference population (namely the target population to which the study therapies are addressed) and homogeneous across the three randomized arms.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	83		
Male	169		
ECOG Performance Status			
Patients were required to have an Eastern Cooperative Oncology Group Performance Status of 0 or 1 (0 = Fully active, able to carry on all pre-disease performance without restriction; 1 =			

Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work)			
Units: Subjects			
0 - Fully active, able to carry on...	198		
1 - Restricted in physically strenuous activity...	54		
Cisplatin Dose categorical			
In this study, chemotherapy-naïve patients received high-dose cisplatin (≥70 mg/m2) either alone or in combination with antineoplastic agents with low or minimal emetogenic potential. Only one patient (in the Arm C) received cisplatin dose <70 mg/m2.			
Units: Subjects			
Dose = 70 mg/m2	63		
Dose >70 mg/m2	189		
Concomitant Chemotherapy			
Eligible patients were chemotherapy-naïve and scheduled to receive the first course of cisplatin (≥70 mg/m2)-based chemotherapy. Patients could receive cisplatin either alone or in combination with antineoplastic agents with low or minimal emetogenic potential.			
Units: Subjects			
Pemetrexed	123		
Gemcitabine	65		
Vinorelbine	53		
Other	11		
BMI			
Body Mass Index			
Units: kilogram(s)/square metre			
arithmetic mean			
standard deviation	-		
Cisplatin Dose			
Units: milligram(s)/square metre			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	Intention To Treat Set (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This population contains all the randomized patients. The ITT has been the data set used for producing statistics on disposition, demographic and anamnestic data in addition to the efficacy and safety data. For ITT efficacy analyses, complete analysis sets were obtained by replacing missing efficacy data using the MVTF method whereby missing data are treated as failures.

Subject analysis set title	Per Protocol Set (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

This population contains all the randomized patients without major protocol violations/deviations as determined by the Principal Investigators. The PP was the dataset used, in addition to the ITT set, for the efficacy analyses

Reporting group values	Intention To Treat Set (ITT)	Per Protocol Set (PP)	
Number of subjects	252	228	
Age categorical			
Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Demographic characteristics for the Intention To Treat set appear consistent to those of the standard reference population (namely the target population to which the study therapies are addressed) and homogeneous across the three randomized arms.			
Units: years arithmetic mean standard deviation	±	±	
Gender categorical Units: Subjects			
Female	83		
Male	169		
ECOG Performance Status			
Patients were required to have an Eastern Cooperative Oncology Group Performance Status of 0 or 1 (0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work)			
Units: Subjects			
0 - Fully active, able to carry on...	198		
1 - Restricted in physically strenuous activity...	54		
Cisplatin Dose categorical			
In this study, chemotherapy-naïve patients received high-dose cisplatin (≥70 mg/m2) either alone or in combination with antineoplastic agents with low or minimal emetogenic potential. Only one patient (in the Arm C) received cisplatin dose <70 mg/m2.			
Units: Subjects			
Dose = 70 mg/m2	63		
Dose >70 mg/m2	189		
Concomitant Chemotherapy			
Eligible patients were chemotherapy-naïve and scheduled to receive the first course of cisplatin (≥70 mg/m2)-based chemotherapy. Patients could receive cisplatin either alone or in combination with antineoplastic agents with low or minimal emetogenic potential.			
Units: Subjects			
Pemetrexed	123		
Gemcitabine	65		
Vinorelbine	53		
Other	11		
BMI			
Body Mass Index			
Units: kilogram(s)/square metre arithmetic mean standard deviation	±	±	
Cisplatin Dose Units: milligram(s)/square metre arithmetic mean standard deviation	±	±	

End points

End points reporting groups

Reporting group title	Arm A (or DEX1 arm)
Reporting group description:	
Treatment arm A: On day 1 oral NEPA and intravenous dexamethasone 12 mg. No further anti-emetic prophylaxis on days 2 thorough 4.	
Reporting group title	Arm B (or DEX3 arm)
Reporting group description:	
Treatment arm B: On day 1 oral NEPA and intravenous dexamethasone 12 mg. Oral dexamethasone 4 mg once per day in the morning of days 2 and 3.	
Reporting group title	Arm C (or DEX4 arm)
Reporting group description:	
Treatment arm C: On day 1 oral NEPA and intravenous dexamethasone 12 mg. Oral dexamethasone 4 mg twice per day on days 2 thorough 4.	
Subject analysis set title	Intention To Treat Set (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
This population contains all the randomized patients. The ITT has been the data set used for producing statistics on disposition, demographic and anamnestic data in addition to the efficacy and safety data. For ITT efficacy analyses, complete analysis sets were obtained by replacing missing efficacy data using the MVTF method whereby missing data are treated as failures.	
Subject analysis set title	Per Protocol Set (PP)
Subject analysis set type	Per protocol
Subject analysis set description:	
This population contains all the randomized patients without major protocol violations/deviations as determined by the Principal Investigators. The PP was the dataset used, in addition to the ITT set, for the efficacy analyses	

Primary: Complete Response (CR: no emesis and no rescue medication)

End point title	Complete Response (CR: no emesis and no rescue medication)
End point description:	
The primary endpoint was the proportion of patients achieving CR (no emetic episode and no use of rescue medication) in the overall phase (0–120 hours from the initiation ofthe first cycle of cisplatin-based chemotherapy).	
End point type	Primary
End point timeframe:	
The overall phase (0–120 hours from the initiation of cisplatin).	

End point values	Arm A (or DEX1 arm)	Arm B (or DEX3 arm)	Arm C (or DEX4 arm)	Intention To Treat Set (ITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	84	85	83	252
Units: percent				
number (not applicable)	58	58	57	173

End point values	Per Protocol Set (PP)			

Subject group type	Subject analysis set			
Number of subjects analysed	228			
Units: percent				
number (not applicable)	173			

Statistical analyses

Statistical analysis title	Complete Response Statistical analysis_Arm A vs C

Statistical analysis description:

For a complete responder during the Overall phase, complete response is expected to occur from day 1 (first day of chemotherapy) thorough day 5 of the first cycle chemotherapy. For a complete responder during the Acute phase, complete response is expected to occur on day 1 of the first cycle of chemotherapy. For a complete responder during the Delayed phase, complete response is expected to occur during days 2 thorough 5 of the first cycle of chemotherapy.

Comparison groups	Arm A (or DEX1 arm) v Arm C (or DEX4 arm)
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	≤ 0.025 [2]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.137
upper limit	0.144

Notes:

[1] - The primary efficacy hypothesis was that NEPA plus 1-day DEX and, in a subordinate position, NEPA plus 3-day DEX (Test treatments) were non-inferior to NEPA plus 4-day DEX (Reference treatment) with respect to the proportion of patients who had a complete response. To accomplish this, the lower boundary of the 2-sided 95% confidence interval (CI) on the difference between the CRs (Risk Difference) must be greater than –15% with 15% used as the prefixed non-inferiority threshold.
[2] - One-sided

Statistical analysis title	Complete Response Statistical analysis_Arm B vs C

Statistical analysis description:

For a complete responder during the Overall phase, complete response is expected to occur from day 1 (first day of chemotherapy) thorough day 5 of the first cycle chemotherapy. For a complete responder during the Acute phase, complete response is expected to occur on day 1 of the first cycle of chemotherapy. For a complete responder during the Delayed phase, complete response is expected to occur during days 2 thorough 5 of the first cycle of chemotherapy.

Comparison groups	Arm C (or DEX4 arm) v Arm B (or DEX3 arm)
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	≤ 0.025 [4]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.004

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.145
upper limit	0.136

Notes:

[3] - The primary efficacy hypothesis was that NEPA plus 1-day DEX and, in a subordinate position, NEPA plus 3-day DEX (Test treatments) were non-inferior to NEPA plus 4-day DEX (Reference treatment) with respect to the proportion of patients who had a complete response. To accomplish this, the lower boundary of the 2-sided 95% confidence interval (CI) on the difference between the CRs (Risk Difference) must be greater than –15% with 15% used as the prefixed non-inferiority threshold.
[4] - One-sided

Secondary: Complete Protection (CP: complete response and none or mild nausea)

End point title	Complete Protection (CP: complete response and none or mild nausea)

End point description:

Secondary endpoints included the proportion of patients who achieved a complete protection (CP; no emetic episode, no use of rescue medication, and no more than mild nausea) during the overall, acute (0–24 hours) and delayed (>24–120 hours) phases.

End point type	Secondary

End point timeframe:

During the acute (within 24 hours post-chemotherapy), delayed (days 2 thorough 5) and overall (days 1 thorough 5) phases of the first cycle of cisplatin-based chemotherapy

End point values	Arm A (or DEX1 arm)	Arm B (or DEX3 arm)	Arm C (or DEX4 arm)	Intention To Treat Set (ITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	84	85	83	252
Units: percent				
number (not applicable)	56	51	51	158

End point values	Per Protocol Set (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	228			
Units: percent				
number (not applicable)	158			

Statistical analyses

Statistical analysis title	Complete Protection Statistical analysis_ArmA vs C

Statistical analysis description:

For a patient defined as complete control during the Overall phase, complete control is expected to occur from day 1 (first day of chemotherapy) thorough day 5 of the first cycle chemotherapy. For a complete control during the Acute phase, complete control is expected to occur on day 1 of the first cycle of chemotherapy. For a complete control during the Delayed phase, complete control is expected to occur during days 2 thorough 5 of the first cycle of chemotherapy

Comparison groups	Arm A (or DEX1 arm) v Arm C (or DEX4 arm)
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	≤ 0.025 [6]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.093
upper limit	0.198

Notes:

[5] - The two-sided 95% Confidence Limits of the difference in the proportion (Risk Difference) of complete control were calculated for the Acute, Delayed and Overall phase by resorting to a generalized linear model with identity link function, binomial distribution and using treatment group as dummy covariate.
[6] - One-sided

Statistical analysis title	Complete Protection Statistical analysis_ArmB vs C

Statistical analysis description:

For a patient defined as complete control during the Overall phase, complete control is expected to occur from day 1 (first day of chemotherapy) thorough day 5 of the first cycle chemotherapy. For a complete control during the Acute phase, complete control is expected to occur on day 1 of the first cycle of chemotherapy. For a complete control during the Delayed phase, complete control is expected to occur during days 2 thorough 5 of the first cycle of chemotherapy

Comparison groups	Arm C (or DEX4 arm) v Arm B (or DEX3 arm)
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	≤ 0.025 [8]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.162
upper limit	0.133

Notes:

[7] - The two-sided 95% Confidence Limits of the difference in the proportion (Risk Difference) of complete control were calculated for the Acute, Delayed and Overall phase by resorting to a generalized linear model with identity link function, binomial distribution and using treatment group as dummy covariate.
[8] - One-sided

Secondary: No emetic episodes

End point title	No emetic episodes

End point description:

Secondary endpoints included the proportion of patients with no emetic episodes during the overall, acute (0–24 hours) and delayed (>24–120 hours) phases.

End point type	Secondary

End point timeframe:

During the acute (within 24 hours post-chemotherapy), delayed (days 2 thorough 5) and overall (days 1

End point values	Arm A (or DEX1 arm)	Arm B (or DEX3 arm)	Arm C (or DEX4 arm)	Intention To Treat Set (ITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	84	85	83	252
Units: percent				
number (not applicable)	72	69	75	216

End point values	Per Protocol Set (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	228			
Units: percent				
number (not applicable)	213			

Statistical analyses

Statistical analysis title	No emetic episodes Statistical analysis_Arm A vs C

Statistical analysis description:

For a patient defined as emesis-free during the Overall phase, no emesis is expected to occur from day 1 (first day of chemotherapy) thorough day 5 of the first cycle chemotherapy. For an emesis-free during the Acute phase, no emesis is expected to occur on day 1 of the first cycle of chemotherapy. For an emesis-free during the Delayed phase, no emesis is expected to occur during days 2 thorough 5 of the first cycle of chemotherapy

Comparison groups	Arm A (or DEX1 arm) v Arm C (or DEX4 arm)
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
P-value	≤ 0.025 [10]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.046
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.145
upper limit	0.052

Notes:

[9] - The two-sided 95% Confidence Limits of the difference in the proportion (Risk Difference) of emesis-free were calculated for the Acute, Delayed and Overall phase by resorting to a generalized linear model with identity link function, binomial distribution and using treatment group as dummy covariate.
[10] - One-sided

Statistical analysis title	No emetic episodes Statistical analysis_Arm B vs C

Statistical analysis description:

For a patient defined as emesis-free during the Overall phase, no emesis is expected to occur from day 1 (first day of chemotherapy) thorough day 5 of the first cycle chemotherapy. For an emesis-free during the Acute phase, no emesis is expected to occur on day 1 of the first cycle of chemotherapy. For an emesis-free during the Delayed phase, no emesis is expected to occur during days 2 thorough 5 of the first cycle of chemotherapy

Comparison groups	Arm C (or DEX4 arm) v Arm B (or DEX3 arm)
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	≤ 0.025 [12]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.092
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.196
upper limit	0.013

Notes:

[11] - The two-sided 95% Confidence Limits of the difference in the proportion (Risk Difference) of emesis-free were calculated for the Acute, Delayed and Overall phase by resorting to a generalized linear model with identity link function, binomial distribution and using treatment group as dummy covariate.
[12] - One-sided

Secondary: No nausea

End point title	No nausea

End point description:

Secondary endpoints included the proportion of patients with no nausea during the overall, acute (0–24 hours) and delayed (>24–120 hours) phases.

End point type	Secondary

End point timeframe:

During the acute (within 24 hours post-chemotherapy), delayed (days 2 thorough 5) and overall (days 1 thorough 5) phases of the first cycle of cisplatin-based chemotherapy

End point values	Arm A (or DEX1 arm)	Arm B (or DEX3 arm)	Arm C (or DEX4 arm)	Intention To Treat Set (ITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	84	85	83	252
Units: percent				
number (not applicable)	39	35	47	121

End point values	Per Protocol Set (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	228			
Units: percent				
number (not applicable)	118			

Statistical analyses

Statistical analysis title	No nausea Statistical analysis_Arm A vs C

Statistical analysis description:

For a patient defined without nausea during the Overall phase, nausea graded as "none" according to the Likert scale should occur from day 1 thorough day 5 of the 1st cycle of chemotherapy. For a patient defined without nausea during the Acute phase, nausea graded as "none" should occur on day 1 of the 1st cycle of chemotherapy. For a patient defined without nausea during the Delayed phase, nausea graded as "none" should occur during days 2 thorough 5 of the first cycle of chemotherapy.

Comparison groups	Arm A (or DEX1 arm) v Arm C (or DEX4 arm)
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
P-value	≤ 0.025 [14]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.102
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.253
upper limit	0.049

Notes:

[13] - The two-sided 95% Confidence Limits of the difference in the proportion (Risk Difference) of patient without nausea were calculated for the Acute, Delayed and Overall phase by resorting to a generalized linear model with identity link function, binomial distribution and using treatment group as dummy covariate.
[14] - One-sided

Statistical analysis title	No nausea Statistical analysis_Arm B vs C

Statistical analysis description:

For a patient defined without nausea during the Overall phase, nausea graded as "none" according to the Likert scale should occur from day 1 thorough day 5 of the 1st cycle of chemotherapy. For a patient defined without nausea during the Acute phase, nausea graded as "none" should occur on day 1 of the 1st cycle of chemotherapy. For a patient defined without nausea during the Delayed phase, nausea graded as "none" should occur during days 2 thorough 5 of the first cycle of chemotherapy.

Comparison groups	Arm C (or DEX4 arm) v Arm B (or DEX3 arm)
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
P-value	≤ 0.025 [16]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.155
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.304
upper limit	0.005

Notes:

[15] - The two-sided 95% Confidence Limits of the difference in the proportion (Risk Difference) of patient without nausea were calculated for the Acute, Delayed and Overall phase by resorting to a generalized linear model with identity link function, binomial distribution and using treatment group as dummy covariate.

[16] - One-sided

Secondary: No Significant Nausea (NSN: no more than mild nausea)

End point title	No Significant Nausea (NSN: no more than mild nausea)

End point description:

Secondary endpoints included the proportion of patients with No Significant Nausea (NSN, defined as no more than mild nausea) during the overall, acute (0–24 hours) and delayed (>24–120 hours) phases.

End point type	Secondary

End point timeframe:

During the acute (within 24 hours post-chemotherapy), delayed (days 2 thorough 5) and overall (days 1 thorough 5) phases of the first cycle of cisplatin-based chemotherapy

End point values	Arm A (or DEX1 arm)	Arm B (or DEX3 arm)	Arm C (or DEX4 arm)	Intention To Treat Set (ITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	84	85	83	252
Units: percent				
number (not applicable)	61	56	59	176

End point values	Per Protocol Set (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	228			
Units: percent				
number (not applicable)	173			

Statistical analyses

Statistical analysis title	No Significant Nausea Statistical analysis_A vs C

Statistical analysis description:

Patient’s nausea for the Overall phase is computed using the worst patient score recorded from day 1 (first day of chemotherapy) thorough day 5 of the first cycle of chemotherapy. Patient’s nausea for the Acute phase is computed using the worst patient score recorded on day 1 of the first cycle of chemotherapy. Patient’s nausea for the Delayed phase, is computed using the worst patient score recorded during days 2 thorough 5 of the first cycle of chemotherapy.

Comparison groups	Arm C (or DEX4 arm) v Arm A (or DEX1 arm)

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	non-inferiority[17]
P-value	≤ 0.025 [18]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.1
upper limit	14.7

Notes:

[17] - Descriptive analyses have been done by tabulating absolute and relative frequency through a three-way contingency table: Treatment x Day (Phase) x Nausea Score. For the ITT set, the relative frequencies were calculated on patients with missing data replaced using the MVTF approach.
[18] - One-sided

Statistical analysis title	No Significant Nausea Statistical analysis_B vs C

Statistical analysis description:

Patient's nausea for the Overall phase is computed using the worst patient score recorded from day 1 (first day of chemotherapy) thorough day 5 of the first cycle of chemotherapy. Patient's nausea for the Acute phase is computed using the worst patient score recorded on day 1 of the first cycle of chemotherapy. Patient's nausea for the Delayed phase, is computed using the worst patient score recorded during days 2 thorough 5 of the first cycle of chemotherapy.

Comparison groups	Arm C (or DEX4 arm) v Arm B (or DEX3 arm)
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	non-inferiority[19]
P-value	≤ 0.025 [20]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.4
upper limit	11.1

Notes:

[19] - Descriptive analyses have been done by tabulating absolute and relative frequency through a three-way contingency table: Treatment x Day (Phase) x Nausea Score. For the ITT set, the relative frequencies were calculated on patients with missing data replaced using the MVTF approach.
[20] - One-sided

Secondary: No use of rescue medications

End point title	No use of rescue medications

End point description:

Secondary endpoints included the proportion of patients with no use of rescue medications during the overall, acute (0–24 hours) and delayed (>24–120 hours) phases.

End point type	Secondary

End point timeframe:

During the acute (within 24 hours post-chemotherapy), delayed (days 2 thorough 5) and overall (days 1 thorough 5) phases of the first cycle of cisplatin-based chemotherapy

End point values	Arm A (or DEX1 arm)	Arm B (or DEX3 arm)	Arm C (or DEX4 arm)	Intention To Treat Set (ITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	84	85	83	252
Units: percent				
number (not applicable)	60	61	58	179

End point values	Per Protocol Set (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	228			
Units: percent				
number (not applicable)	178			

Statistical analyses

Statistical analysis title	No use of rescue medications Stat. analysis_A vs C

Statistical analysis description:

For a patient defined as rescue-free during the Overall phase, no salvage therapy intake occurs from day 1 (first day of chemotherapy) thorough day 5 of the first cycle chemotherapy. For a rescue-free during the Acute phase, no salvage therapy intake occurs on day 1 of the first cycle of chemotherapy. For a rescue-free during the Delayed phase, no salvage therapy intake occurs during days 2 thorough 5 of the first cycle of chemotherapy.

Comparison groups	Arm C (or DEX4 arm) v Arm A (or DEX1 arm)
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
P-value	≤ 0.025 [22]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.123
upper limit	0.154

Notes:

[21] - The two-sided 95% Confidence Limits of the difference in the proportion (Risk Difference) of rescue-free were calculated for the Acute, Delayed and Overall phase by resorting to a generalized linear model with identity link function, binomial distribution and using treatment group as dummy covariate.
[22] - One-sided

Statistical analysis title	No use of rescue medications Stat. analysis_B vs C

Statistical analysis description:

For a patient defined as rescue-free during the Overall phase, no salvage therapy intake occurs from day 1 (first day of chemotherapy) thorough day 5 of the first cycle chemotherapy. For a rescue-free

during the Acute phase, no salvage therapy intake occurs on day 1 of the first cycle of chemotherapy. For a rescue-free during the Delayed phase, no salvage therapy intake occurs during days 2 thorough 5 of the first cycle of chemotherapy.

Comparison groups	Arm C (or DEX4 arm) v Arm B (or DEX3 arm)
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	non-inferiority[23]
P-value	≤ 0.025 [24]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.019
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.119
upper limit	0.156

Notes:

[23] - The two-sided 95% Confidence Limits of the difference in the proportion (Risk Difference) of rescue-free were calculated for the Acute, Delayed and Overall phase by resorting to a generalized linear model with identity link function, binomial distribution and using treatment group as dummy covariate.
[24] - One-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The overall study period until follow up visit (within 30 days from randomization)

Adverse event reporting additional description:

Adverse events were evaluated by the investigators according to the Common Terminology Criteria for Adverse Events.
Information about every adverse event/reaction have been collected and recorded in the Adverse Event electronic Case Report Form.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Arm A (or DEX1 arm)

Reporting group description:

Treatment arm A: On day 1 oral NEPA and intravenous dexamethasone 12 mg.
No further anti-emetic prophylaxis on days 2 thorough 4.

Reporting group title	Arm B (or DEX3 arm)

Reporting group description:

Treatment arm B: On day 1 oral NEPA and intravenous dexamethasone 12 mg.
Oral dexamethasone 4 mg once per day in the morning of days 2 and 3.

Reporting group title	Arm C (or DEX4 arm)

Reporting group description:

Treatment arm C: On day 1 oral NEPA and intravenous dexamethasone 12 mg.
Oral dexamethasone 4 mg twice per day on days 2 thorough 4.

Serious adverse events	Arm A (or DEX1 arm)	Arm B (or DEX3 arm)	Arm C (or DEX4 arm)
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 80 (7.50%)	5 / 84 (5.95%)	3 / 81 (3.70%)
number of deaths (all causes)	3	1	2
number of deaths resulting from adverse events	3	0	1
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammatory marker increased			

alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood electrolytes abnormal			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Acute coronary syndrome			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	2 / 80 (2.50%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Peripheral ischaemia			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Brain stem stroke			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Pancytopenia			
alternative dictionary used: MedDRA 20.1			

subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumomediastinum			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm A (or DEX1 arm)	Arm B (or DEX3 arm)	Arm C (or DEX4 arm)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 80 (62.50%)	56 / 84 (66.67%)	53 / 81 (65.43%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 80 (0.00%)	2 / 84 (2.38%)	1 / 81 (1.23%)
occurrences (all)	0	2	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	0 / 80 (0.00%)	2 / 84 (2.38%)	1 / 81 (1.23%)
occurrences (all)	0	2	1
Phlebitis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Thromboembolic event			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	1 / 80 (1.25%)	2 / 84 (2.38%)	1 / 81 (1.23%)
occurrences (all)	1	2	1
Fatigue			
subjects affected / exposed	16 / 80 (20.00%)	19 / 84 (22.62%)	22 / 81 (27.16%)
occurrences (all)	17	20	23
Fever			
subjects affected / exposed	1 / 80 (1.25%)	2 / 84 (2.38%)	4 / 81 (4.94%)
occurrences (all)	1	2	4
Allergic reaction to mannitol			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1

Asthenia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Bilateral hypoacusia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Drowsiness			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Dysphonia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Eyestrain			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
General decay			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Haemoptysis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Hiccough			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Pain at right shoulder			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Pain in the right palm			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Panic attack			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Scapular pain			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0

Surgical site pain			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Sweating			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	2	0
Irritability			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Localised oedema			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	3 / 80 (3.75%)	4 / 84 (4.76%)	2 / 81 (2.47%)
occurrences (all)	3	4	2
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	2 / 81 (2.47%)
occurrences (all)	0	1	3
Cough			
subjects affected / exposed	2 / 80 (2.50%)	5 / 84 (5.95%)	2 / 81 (2.47%)
occurrences (all)	2	5	2
Dyspnoea			
subjects affected / exposed	3 / 80 (3.75%)	4 / 84 (4.76%)	1 / 81 (1.23%)
occurrences (all)	3	4	1
Hoarseness			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Pharyngeal mucositis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Cooling syndrome	Additional description: Episode of cooling syndrome		

subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Nasal discharge			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Sore throat			
subjects affected / exposed	0 / 80 (0.00%)	2 / 84 (2.38%)	0 / 81 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	0 / 80 (0.00%)	2 / 84 (2.38%)	0 / 81 (0.00%)
occurrences (all)	0	2	0
Insomnia			
subjects affected / exposed	1 / 80 (1.25%)	1 / 84 (1.19%)	4 / 81 (4.94%)
occurrences (all)	1	1	4
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 80 (2.50%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	2	0	0
Thrombocytosis			
subjects affected / exposed	2 / 80 (2.50%)	2 / 84 (2.38%)	1 / 81 (1.23%)
occurrences (all)	2	2	1
Blood bilirubin increased			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Creatinine increased			
subjects affected / exposed	1 / 80 (1.25%)	2 / 84 (2.38%)	5 / 81 (6.17%)
occurrences (all)	1	2	5
Weight loss			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	2 / 81 (2.47%)
occurrences (all)	0	1	2
white blood cell decreased			

subjects affected / exposed	1 / 80 (1.25%)	3 / 84 (3.57%)	2 / 81 (2.47%)
occurrences (all)	1	3	2
Neutrophil count decreased			
subjects affected / exposed	6 / 80 (7.50%)	4 / 84 (4.76%)	5 / 81 (6.17%)
occurrences (all)	6	5	5
Platelet count decreased			
subjects affected / exposed	4 / 80 (5.00%)	3 / 84 (3.57%)	1 / 81 (1.23%)
occurrences (all)	4	4	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Worsening of hypertension			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Chest pain - cardiac			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Sinus bradycardia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	0 / 80 (0.00%)	2 / 84 (2.38%)	3 / 81 (3.70%)
occurrences (all)	0	2	3
Headache			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	1 / 81 (1.23%)
occurrences (all)	0	1	1
Confusional state			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			

subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Paresthesia			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Presyncope			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	1 / 80 (1.25%)	1 / 84 (1.19%)	1 / 81 (1.23%)
occurrences (all)	1	1	1
Tremor			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 80 (5.00%)	2 / 84 (2.38%)	4 / 81 (4.94%)
occurrences (all)	4	2	4
Neutropenia			
subjects affected / exposed	1 / 80 (1.25%)	3 / 84 (3.57%)	1 / 81 (1.23%)
occurrences (all)	1	3	1
Thrombocytopenia			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Febrile neutropenia			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Leukocytosis			
subjects affected / exposed	1 / 80 (1.25%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	1	1	0
Ear and labyrinth disorders			
Bilateral hearing loss			

subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Hearing impaired			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Tinnitus			
subjects affected / exposed	2 / 80 (2.50%)	2 / 84 (2.38%)	1 / 81 (1.23%)
occurrences (all)	2	3	1
Vertigo			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	1 / 81 (1.23%)
occurrences (all)	0	1	1
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	2 / 81 (2.47%)
occurrences (all)	1	0	2
Lachrymation			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Anal pain			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Bloating			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	13 / 80 (16.25%)	10 / 84 (11.90%)	21 / 81 (25.93%)
occurrences (all)	13	10	21
Diarrhoea			
subjects affected / exposed	2 / 80 (2.50%)	2 / 84 (2.38%)	4 / 81 (4.94%)
occurrences (all)	2	2	4
Dyspepsia			
subjects affected / exposed	1 / 80 (1.25%)	2 / 84 (2.38%)	1 / 81 (1.23%)
occurrences (all)	1	2	1
Esophageal pain			

subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	2 / 81 (2.47%)
occurrences (all)	0	1	2
Gastritis			
subjects affected / exposed	4 / 80 (5.00%)	2 / 84 (2.38%)	3 / 81 (3.70%)
occurrences (all)	4	2	3
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 80 (1.25%)	2 / 84 (2.38%)	0 / 81 (0.00%)
occurrences (all)	1	2	0
Burning at the throat			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Epigastralgia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Hiccups			
subjects affected / exposed	1 / 80 (1.25%)	1 / 84 (1.19%)	3 / 81 (3.70%)
occurrences (all)	1	1	3
Hyporexia			
subjects affected / exposed	0 / 80 (0.00%)	2 / 84 (2.38%)	0 / 81 (0.00%)
occurrences (all)	0	2	0
Retching			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Gastrointestinal pain			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Mucositis oral			
subjects affected / exposed	1 / 80 (1.25%)	4 / 84 (4.76%)	5 / 81 (6.17%)
occurrences (all)	1	4	5
Nausea			
subjects affected / exposed	8 / 80 (10.00%)	12 / 84 (14.29%)	7 / 81 (8.64%)
occurrences (all)	10	12	10
Oral pain			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Vomiting			

subjects affected / exposed	3 / 80 (3.75%)	2 / 84 (2.38%)	0 / 81 (0.00%)
occurrences (all)	3	2	0
Hepatobiliary disorders			
Alkaline phospatase increased			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 80 (1.25%)	1 / 84 (1.19%)	1 / 81 (1.23%)
occurrences (all)	1	1	1
Erythema multiforme			
subjects affected / exposed	1 / 80 (1.25%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	1	1	0
Rash acneiform			
subjects affected / exposed	0 / 80 (0.00%)	2 / 84 (2.38%)	1 / 81 (1.23%)
occurrences (all)	0	2	1
Rash			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	1 / 81 (1.23%)
occurrences (all)	0	1	1
Rash pruritic	Additional description: Pruritic papular erythematous rash		
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Haematuria			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Renal colic			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	1 / 80 (1.25%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	1	1	0
Bone pain			
subjects affected / exposed	1 / 80 (1.25%)	3 / 84 (3.57%)	2 / 81 (2.47%)
occurrences (all)	1	3	2
Chest wall trauma			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Cold legs			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Lumbar spinal back pain			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Pain	Additional description: Pain in the right-hand parascapular region		
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Osteoporosis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Device related infection			

subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Mucosal infection			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 80 (1.25%)	1 / 84 (1.19%)	2 / 81 (2.47%)
occurrences (all)	1	1	2
Hyperglycaemia			
subjects affected / exposed	0 / 80 (0.00%)	2 / 84 (2.38%)	1 / 81 (1.23%)
occurrences (all)	0	2	1
Hyperkalaemia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Cachexia			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Inappetance			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2018	The amendment ("LUNG-NEPA_EM2 del 29.08.2018") regarded these aspects: • extension of the trial duration, with an extension of the enrollment phase from 18 months to 48 months, in order to allow the achievement of the number of patients foreseen by the study protocol; • reformulation of the statistical methodology, on the basis of the new evidence available on the dexamethasone-sparing strategy in the setting of single-day HEC. The LUNG-NEPA study was initially planned with a composite "Study Win Criteria" consisting in declaring study success if non-inferiority will be achieved in at least one of the following two comparisons: "NEPA plus 3-day DEX vs. NEPA plus 4-day DEX" or "NEPA plus 1-day DEX vs. NEPA plus 4-day DEX". With this amendment: - the "Study Win Criteria" remained unchanged but it was introduced the prioritization between the two comparisons, as suggested by the experts: 1) "NEPA plus 1-day DEX vs. NEPA plus 4-day DEX" and, in a subordinate position, 2) "NEPA plus 3-day DEX vs. NEPA plus 4-day DEX"; - the sample size changed from 588 patients (196 in each arm) to 468 patients (156 in each treatment arm), in order to have 450 enrolled patients (150 in each treatment arm), considering a 4% ineligibility rate. - the primary efficacy hypothesis changed as follows: NEPA plus 1-day DEX and, in a subordinate position, NEPA plus 3-day DEX (Test treatments) were non-inferior to NEPA plus 4-day DEX (Reference treatment) with respect to the proportion of patients who had a complete response (CR; defined as no emetic episodes, and no rescue medication use during the overall phase of the first chemotherapy cycle).
11 December 2019	The amendment ("LUNG-NEPA_EM3 del 21.11.2019") regarded these aspects: • adaptation of the statistical methodology, in the light of the new evidence available on the dexamethasone-sparing strategy in the CINV (chemotherapy-induced nausea and vomiting) prevention [Ito et al. J Clin Oncol 2018; 36: 1000-1006], The non-inferiority margin was set at -15% difference (DEX1 or DEX3 minus DEX4) instead the previous -10%. The study protocol was amended as follows: The primary efficacy hypothesis was that NEPA plus 1-day DEX and, in a subordinate position, NEPA plus 3-day DEX (Test treatments) were non-inferior to NEPA plus 4-day DEX (Reference treatment) with respect to the proportion of patients who had a complete response. To accomplish this, the lower boundary of the 2-sided 95% confidence interval (CI) on the difference between the CRs (Risk Difference) was to be greater than –15% with 15% used as the prefixed non-inferiority threshold. A sample size of 210 eligible and assessable patients when randomized in a 1:1:1 ratio (that is 70 patients in each arm) achieved 80% power to detect a noninferiority margin equal to 15% in the prioritized comparison "DEX1 arm vs. DEX4 arm" assuming that the proportion of CR during the overall phase would be 90% in the reference arm [9] and a one-sided type I error rate equal to 0.025. Assuming an attrition rate of 4%, at least 73 eligible and assessable patients per arm needed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

1.Unblinding; however, the consistency of overall findings supports the validity of the study results.
2.Females represented only 33% of study population; however, this is consistent with recent evidence regarding patients undergoing cisplatin chemo

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34101934