Clinical trial results:
The BEACON Study (BrEAst Cancer Outcomes with NKTR-102): A Phase 3 Open-Label, Randomized, Multicenter Study of NKTR-102 versus Treatment of Physician's Choice (TPC) in Patients with Locally Recurrent or Metastatic Breast Cancer Previously Treated with an Anthracycline, a Taxane, and Capecitabine

Summary

EudraCT number	2011-003832-30
Trial protocol	BE GB DE ES NL IT
Global end of trial date	08 April 2016

Results information

Result version number	v1 (current)
This version publication date	05 August 2017
First version publication date	05 August 2017

Trial information

Trial identification

Sponsor protocol code	11-PIR-11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01492101
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Nektar Therapeutics
Sponsor organisation address	455 Mission Bay Boulevard South, San Francisco, United States, CA 94158
Public contact	Clinical Trial Information Desk, Quintiles Contact Center, +1 862 261 3634, StudyInquiry@nektar.com
Scientific contact	Clinical Trial Information Desk, Quintiles Contact Center, +1 862 261 3634, StudyInquiry@nektar.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	12 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the overall survival (OS) of subjects who received NKTR-102 given once every 21 days to subjects who received treatment of physician's choice (TPC) selected from the following list of 7 single-agent intravenous (IV) therapies: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel.

Protection of trial subjects:

This study was carried out in compliance with the protocol and in accordance with standard operating procedures. These were designed to ensure adherence to Good Clinical Practice, as described in the following documents: International Council for Harmonisation Harmonized Tripartite Guidelines for Good Clinical Practice 1996; United States 21 Code of Federal Regulations dealing with clinical studies (including Parts 50 and 56 concerning informed consent and Institutional Review Board regulations, and parts 54 and 312); Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West, South Africa 1996, Edinburgh 2000, Washington 2002, Tokyo 2004, Seoul 2008).

Background therapy: -

Evidence for comparator:

The TPC control arm consisted of a choice of one of the following 7 therapies: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel. Oncologists have a relatively broad range of potential chemotherapies that demonstrate some anti-cancer activity in the treatment of subjects with advanced breast cancer whose disease has progressed following therapy with anthracycline, a taxane, and capecitabine (ATC). Factors affecting the choice are often balanced between efficacy, toxicity, and treatment schedule and are based on tumor and subject characteristics, subject preference, and health care/regulatory and economics policies. Because there is no consensus in the oncology community on a single standard of care for advanced breast cancer subjects who have progressed after treatment with ATC (particularly across the countries that participated in this trial) and these 7 drugs are all routinely used in the treatment of advanced breast cancer, the TPC arm represented the current best chemotherapeutic standard of care. Anthracyclines (such as doxorubicin) and capecitabine, are also commonly used in the treatment of advanced breast cancer; however, they were not included as TPC drugs because this subject population had, per the inclusion criteria, already been treated with these and may have been refractory.

Actual start date of recruitment	19 December 2011
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	Netherlands: 2
Country: Number of subjects enrolled	Spain: 97
Country: Number of subjects enrolled	United Kingdom: 42
Country: Number of subjects enrolled	Belgium: 92

Country: Number of subjects enrolled	France: 83
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	United States: 378
Country: Number of subjects enrolled	Canada: 24
Country: Number of subjects enrolled	Russian Federation: 23
Country: Number of subjects enrolled	Korea, Republic of: 85
Worldwide total number of subjects	852
EEA total number of subjects	342

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)	683
From 65 to 84 years	169
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects had histologically or cytologically confirmed carcinoma of the breast; received a minimum of 2 and a maximum of 5 prior cytotoxic chemotherapy regimens for the treatment of locally recurrent or metastatic breast cancer, with the last dose of cytotoxic chemotherapy administered within 6 months of the date of randomization into this trial.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	NKTR-102

Arm description:

NKTR-102 for injection was administered as an IV infusion over 90 ± 15 minutes, on Day 1 of each 21-day cycle) at a dose level of 145 mg/m^2.

Arm type	Experimental
Investigational medicinal product name	NKTR-102
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

NKTR-102 was administered as an IV infusion over 90 ± 15 minutes, on Day 1 of each 21-day cycle at a dose level of 145 mg/m^2. Body surface area was determined based on baseline height and current weight before the start of each cycle. The NKTR-102 was formulated as a sterile lyophilised powder of NKTR-102 in lactate buffer at pH 3.5. NKTR-102 for injection was reconstituted with commercially available 5% dextrose injection. Specific NKTR-102 dose modifications could be made for drug-related neutropenia, thrombocytopenia, anaemia, diarrhoea, dehydration, nausea/vomiting/abdominal pain and other drug-related, non-haematological toxicities. Trial drug was continued until disease progression, unacceptable toxicity, death, withdrawal by subject, Principal Investigator decision, lost to follow-up, protocol violation, or trial termination by Sponsor.

Arm title	TPC drugs

Arm description:

The TPC drugs were administered in 21- or 28-day treatment cycles, depending on the institutional guidelines for the specific drug. The dosage and administration of the TPC drugs followed the institutional guidelines provided for each agent, with the exception of: Eribulin, which was administered in accordance with its local country Summary of Product Characteristics (SmPC) or Prescribing Information OR initially administered at no less than 1.4 mg/m^2 on Days 1 and 8 every 21 days; Ixabepilone, which was initially administered at 40 mg/m2 on Day 1 every 21 days, then per institutional guidelines.

Arm type	Active comparator
Investigational medicinal product name	TPC
Investigational medicinal product code	
Other name	Made up of 1 of 7 single-agent IV chemotherapies
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The TPC drugs were administered in 21- or 28-day treatment cycles, depending on the institutional

guidelines for the specific drug. Some TPC drugs could be administered at weekly intervals. Body surface area was determined before the start of each cycle, based on baseline height and most recent weight. The dosage and administration of the TPC drugs followed the institutional guidelines provided for each agent, with the exception of: Eribulin which was administered in accordance with its local country SmPC or Prescribing Information or initially administered at no less than 1.4 mg/m^2 on Days 1 and 8 every 21 days; and Ixabepilone which was initially administered at 40 mg/m^2 on Day 1 every 21 days, then per institutional guidelines.

Number of subjects in period 1	NKTR-102	TPC drugs
Started	429	423
Completed	92	81
Not completed	337	342
Consent withdrawn by subject	14	18
Death	323	322
Lost to follow-up	-	2

Baseline characteristics

Reporting groups	
Reporting group title	NKTR-102
Reporting group description:	
NKTR-102 for injection was administered as an IV infusion over 90 ± 15 minutes, on Day 1 of each 21-day cycle) at a dose level of 145 mg/m^2.	
Reporting group title	TPC drugs
Reporting group description:	
The TPC drugs were administered in 21- or 28-day treatment cycles, depending on the institutional guidelines for the specific drug. The dosage and administration of the TPC drugs followed the institutional guidelines provided for each agent, with the exception of: Eribulin, which was administered in accordance with its local country Summary of Product Characteristics (SmPC) or Prescribing Information OR initially administered at no less than 1.4 mg/m^2 on Days 1 and 8 every 21 days; Ixabepilone, which was initially administered at 40 mg/m2 on Day 1 every 21 days, then per institutional guidelines.	

Reporting group values	NKTR-102	TPC drugs	Total
Number of subjects	429	423	852
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	341	342	683
From 65-84 years	88	81	169
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	55.1	55.2	
standard deviation	± 10.29	± 10.1	-
Gender categorical Units: Subjects			
Female	429	423	852
Male	0	0	0

End points

End points reporting groups

Reporting group title	NKTR-102

Reporting group description:

NKTR-102 for injection was administered as an IV infusion over 90 ± 15 minutes, on Day 1 of each 21-day cycle) at a dose level of 145 mg/m^2.

Reporting group title	TPC drugs

Reporting group description:

The TPC drugs were administered in 21- or 28-day treatment cycles, depending on the institutional guidelines for the specific drug. The dosage and administration of the TPC drugs followed the institutional guidelines provided for each agent, with the exception of: Eribulin, which was administered in accordance with its local country Summary of Product Characteristics (SmPC) or Prescribing Information OR initially administered at no less than 1.4 mg/m^2 on Days 1 and 8 every 21 days; Ixabepilone, which was initially administered at 40 mg/m2 on Day 1 every 21 days, then per institutional guidelines.

Primary: Kaplan-Meier Estimate of OS: Intention to Treat (ITT) Population

End point title	Kaplan-Meier Estimate of OS: Intention to Treat (ITT) Population

End point description:

Duration of OS was defined as the time from the date of randomisation to the date of death due to any cause. Subjects were followed until their date of death, loss to follow-up, withdrawal of consent for further follow-up for survival, or final database closure. OS was determined using the ITT population which included all subjects randomised into 1 of the 2 treatment arms. Subjects who were lost-to-follow-up or were not known to have died were censored at last date they were shown to be alive. Subjects who did not have any follow-up since the date of randomisation were censored at the date of randomization.

End point type	Primary

End point timeframe:

From randomisation to death, loss to follow-up, withdrawal of consent for further follow-up for survival, or final database closure.

End point values	NKTR-102	TPC drugs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	429	423		
Units: Months				
median (confidence interval 95%)	12.4 (11 to 13.6)	10.3 (9 to 11.3)		

Statistical analyses

Statistical analysis title	Analysis of OS
Comparison groups	NKTR-102 v TPC drugs

Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.0835
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.872
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.747
upper limit	1.019

Notes:

[1] - Two-sided log-rank test, stratified by geographic region, prior use of eribulin, and receptor status.

Secondary: Kaplan-Meier Estimate of Progression-Free Survival (PFS): ITT Population

End point title	Kaplan-Meier Estimate of Progression-Free Survival (PFS): ITT Population

End point description:

PFS was defined as the time from the date of randomisation to the earliest date of disease progression (assessed by the investigator according to RECIST version 1.1) or death due to any cause. PFS was determined using the ITT population which included all subjects randomised into 1 of the 2 treatment arms. For subjects whose disease did not progress or who did not die, the PFS time was censored at the time of the last tumor assessment that demonstrated lack of disease progression. For subjects who received new anti-cancer therapy, the PFS time was censored at the start of the new anti-cancer therapy.

End point type	Secondary

End point timeframe:

Every 8 weeks (± 7 days) from date of randomisation until earliest documented disease progression or death.

End point values	NKTR-102	TPC drugs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	429	423		
Units: Months				
median (confidence interval 95%)	2.4 (2.1 to 3.5)	2.8 (2.1 to 3.5)		

Statistical analyses

Statistical analysis title	Analysis of PFS
Comparison groups	NKTR-102 v TPC drugs

Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3017
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.926
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.798
upper limit	1.075

Secondary: Clinical benefit rate (CBR): ITT Population

End point title	Clinical benefit rate (CBR): ITT Population

End point description:

CBR was defined as the proportion of subjects with a CR, PR, or stable disease (SD) for at least 6 months (≥ 182 days).

End point type	Secondary

End point timeframe:

At least 6 months (≥ 182 days).

End point values	NKTR-102	TPC drugs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	429	423		
Units: Percentage of subjects				
number (confidence interval 95%)	20.5 (16.8 to 24.6)	19.6 (15.9 to 23.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR): Efficacy Evaluable Population

End point title	Duration of response (DOR): Efficacy Evaluable Population

End point description:

DOR was defined as the time from first documented CR or PR until the earliest evidence of disease progression or death from any cause. Subjects who were alive without documented disease progression per RECIST version 1.1 were censored at the date of last tumor assessment without disease progression or start of new anti-cancer therapy for the study disease.

End point type	Secondary

End point timeframe:

From the time measurement criteria for CR/PR (whichever was first recorded) were first met until the first date that recurrent disease or disease progression or death was objectively documented.

End point values	NKTR-102	TPC drugs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	358		
Units: Months				
median (confidence interval 95%)	3.9 (3.5 to 5.1)	3.7 (2.1 to 3.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Dose Reductions: Safety Population

End point title	Incidence of Dose Reductions: Safety Population

End point description:

Proportion of subjects who had a reduction in dose.

End point type	Secondary

End point timeframe:

All cycles.

End point values	NKTR-102	TPC drugs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	425	406		
Units: Percentage of subjects				
number (not applicable)	27.5	28.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life Questionnaire-Core 30 (QLQ-C30) individual scale, overall score: ITT Population

End point title	Quality of Life Questionnaire-Core 30 (QLQ-C30) individual scale, overall score: ITT Population

End point description:

The QLQ-C30 is composed of 5 multi-item functional scales (physical, role, social, emotional and cognitive functioning), a global health status/QoL scale, 3 symptom scales (fatigue, nausea/vomiting, and pain), and 6 single items (financial impact, appetite loss, diarrhoea, constipation, insomnia and dyspnoea). Most items are scaled 1 to 4 except the items contributing to the global health status/QoL, which are 7-point questions. Raw scores were transformed using a linear transformation to standardise the results so that scores range from 0 to 100. n=number of subjects who completed each individual scale.

End point type	Secondary

End point timeframe:

Baseline

End point values	NKTR-102	TPC drugs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	429	423		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Global health status/QoL (n=421;405)	61.4 (± 21.76)	58 (± 20.43)		
Physical functioning (n=422;406)	74.5 (± 19.72)	72.3 (± 19.74)		
Role functioning (n=422;405)	71.8 (± 26.81)	67.3 (± 26.93)		
Emotional functioning (n=421;405)	72.4 (± 21.86)	71.9 (± 20.06)		
Cognitive functioning (n=421;405)	82.5 (± 18.7)	81.2 (± 19.04)		
Social functioning (n=421;405)	73 (± 26.69)	71 (± 25.06)		
Fatigue (n=422;406)	37.7 (± 23.68)	41.3 (± 22.98)		
Nausea and vomiting (n=422;406)	8.6 (± 13.39)	9.9 (± 16.17)		
Pain (n=422;406)	32.3 (± 27.2)	35.3 (± 28.01)		
Dyspnoea (n=421;406)	24.5 (± 27.44)	23.6 (± 26.2)		
Insomnia (n=421;406)	29.3 (± 28.94)	31.5 (± 27.11)		
Appetite loss (n=422;406)	24.3 (± 27.55)	26.6 (± 27.89)		
Constipation (n=422;403)	18 (± 25.9)	21 (± 28.15)		
Diarrhoea (n=421;404)	6.3 (± 13.64)	5.6 (± 11.14)		
Financial difficulties (n=421;404)	26.4 (± 31.29)	21.9 (± 28.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: QLQ-C30 individual scale, change over time: ITT Population

End point title	QLQ-C30 individual scale, change over time: ITT Population

End point description:

The QLQ-C30 is composed of 5 multi-item functional scales (physical, role, social, emotional and cognitive functioning), a global health status/QoL scale, 3 symptom scales (fatigue, nausea/vomiting, and pain), and 6 single items (financial impact, appetite loss, diarrhea, constipation, insomnia and dyspnea). Most items are scaled 1 to 4 except the items contributing to the global health status/QoL, which are 7-point questions. Raw scores were transformed using a linear transformation to standardise the results so that scores range from 0 to 100. n=number of subjects who completed each individual scale. Because the number of patients that completed the HRQoL questionnaires decreased to below 10% of the population beyond 32 weeks, meaningful HRQoL analyses were not reliable after Week 32.

End point type	Secondary

End point timeframe:

From Baseline to Week 8, Week 16, Week 24, Week 32, Week 40, Week 48, Week 56.

End point values	NKTR-102	TPC drugs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	429	423		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Global health status/QoL: Week 8 (n=337;311)	-4.4 (± 22.57)	-4.7 (± 20.37)		
Global health status/QoL: Week 16 (n=181;159)	-2.5 (± 22.9)	-5.6 (± 21.86)		
Global health status/QoL: Week 24 (n=116;90)	-1.8 (± 24.99)	-6.6 (± 22.47)		
Global health status/QoL: Week 32 (n=69;59)	-0.2 (± 20.39)	-6.3 (± 26.66)		
Global health status/QoL: Week 40 (n=48;31)	-5.2 (± 22.27)	-2.6 (± 19.41)		
Global health status/QoL: Week 48 (n=29;19)	-2.3 (± 18.62)	-1.8 (± 20.71)		
Global health status/QoL: Week 56 (n=26;15)	2.9 (± 17.79)	-11.1 (± 29.36)		
Physical functioning: Week 8 (n=340;315)	-4.9 (± 17.98)	-7.1 (± 17.4)		
Physical functioning: Week 16 (n=181;159)	-3 (± 20.63)	-7 (± 18.26)		
Physical functioning: Week 24 (n=116;92)	0.3 (± 20.93)	-4.7 (± 15.9)		
Physical functioning: Week 32 (n=68;60)	-3 (± 18.88)	-8.5 (± 20.4)		
Physical functioning: Week 40 (n=48;31)	-1.9 (± 19.23)	-6.4 (± 18.81)		
Physical functioning: Week 48 (n=30;19)	0.2 (± 17.66)	-7.4 (± 16.46)		
Physical functioning: Week 56 (n=26;16)	2.2 (± 13.48)	-10.4 (± 24.28)		
Role functioning: Week 8 (n=340;314)	-6.6 (± 27.26)	-8.3 (± 27.37)		
Role functioning: Week 16 (n=180;159)	-4.8 (± 26.06)	-8.3 (± 24.41)		
Role functioning: Week 24 (n=116;91)	-7.8 (± 33.3)	-10.8 (± 26.72)		
Role functioning: Week 32 (n=68;60)	-9.7 (± 19.03)	-12.2 (± 29.81)		
Role functioning: Week 40 (n=48;30)	-8.7 (± 30.94)	-7.8 (± 27.93)		
Role functioning: Week 48 (n=30;19)	-3.1 (± 25.38)	-5.7 (± 21.7)		
Role functioning: Week 56 (n=26;16)	-2.6 (± 17.12)	-9.4 (± 35.08)		
Emotional functioning: Week 8 (n=338;313)	-0.5 (± 19.65)	-2 (± 19.95)		
Emotional functioning: Week 16 (n=181;160)	2.7 (± 18.93)	-1.6 (± 20.57)		
Emotional functioning: Week 24 (n=116;91)	-0.6 (± 22.34)	-3.7 (± 18.95)		
Emotional functioning: Week 32 (n=69;59)	-2.8 (± 21.02)	-7.6 (± 20.88)		
Emotional functioning: Week 40 (n=48;31)	-1.4 (± 26.12)	0.8 (± 19.11)		
Emotional functioning: Week 48 (n=29;19)	0.9 (± 21.37)	1.2 (± 18.83)		
Emotional functioning: Week 56 (n=26;15)	-3.6 (± 19.72)	-4.7 (± 25.29)		
Cognitive functioning: Week 8 (n=339,313)	-3.3 (± 18.46)	-3.2 (± 19.44)		
Cognitive functioning: Week 16 (n=181,160)	-1.4 (± 17.67)	-4.4 (± 20.81)		

Cognitive functioning: Week 24 (n=116,91)	-1.8 (± 17.26)	-2.2 (± 17.12)		
Cognitive functioning: Week 32 (n=69,59)	-4.6 (± 17.82)	-7.9 (± 20.14)		
Cognitive functioning: Week 40 (n=48,31)	-5.7 (± 18.61)	-3.5 (± 21.6)		
Cognitive functioning: Week 48 (n=29,19)	-4.6 (± 18.04)	2.2 (± 17.75)		
Cognitive functioning: Week 56 (n=26,15)	-2.9 (± 18.25)	-6.7 (± 22.97)		
Social functioning: Week 8 (n=339,313)	-4.9 (± 27.46)	-6.2 (± 24.04)		
Social functioning: Week 16 (n=181,160)	0.4 (± 27.57)	-6.4 (± 24.2)		
Social functioning: Week 24 (n=116,90)	-3.4 (± 25.68)	-7.2 (± 24.1)		
Social functioning: Week 32 (n=69,59)	-8.8 (± 20.61)	-7.2 (± 30.1)		
Social functioning: Week 40 (n=48,31)	-9.7 (± 26.09)	-7 (± 20.98)		
Social functioning: Week 48 (n=29,19)	-5.5 (± 17.86)	-6.6 (± 20.71)		
Social functioning: Week 56 (n=26,15)	-3.2 (± 22.25)	-24.4 (± 29.96)		
Fatigue: Week 8 (n=340,315)	6.7 (± 22.88)	6.6 (± 22.17)		
Fatigue: Week 16 (n=180,161)	3.7 (± 22.63)	7.7 (± 22.84)		
Fatigue: Week 24 (n=116,92)	3 (± 26.51)	3.6 (± 21.23)		
Fatigue: Week 32 (n=69,60)	5 (± 21.84)	6.6 (± 24.25)		
Fatigue: Week 40 (n=48,31)	4.1 (± 26.65)	2.3 (± 19.02)		
Fatigue: Week 48 (n=30,19)	0.9 (± 18.69)	6.7 (± 14.53)		
Fatigue: Week 56 (n=26,16)	2.1 (± 19.57)	4.5 (± 24.36)		
Nausea and vomiting: Week 8 (n=340,315)	12.8 (± 23.28)	4.2 (± 21.94)		
Nausea and vomiting: Week 16 (n=180,160)	8.8 (± 19.85)	-2 (± 19.1)		
Nausea and vomiting: Week 24 (n=116,92)	7.2 (± 22.57)	-0.1 (± 16.55)		
Nausea and vomiting: Week 32 (n=69,60)	6.5 (± 14.21)	3.5 (± 18.81)		
Nausea and vomiting: Week 40 (n=48,31)	4.5 (± 12.97)	5.6 (± 23.61)		
Nausea and vomiting: Week 48 (n=30,19)	5 (± 13.77)	3.9 (± 28.92)		
Nausea and vomiting: Week 56 (n=26,16)	8 (± 11.66)	1.6 (± 23.02)		
Pain: Week 8 (n=341,315)	-1.7 (± 26.08)	2.4 (± 27.03)		
Pain: Week 16 (n=182,161)	-5 (± 26.9)	1.9 (± 27.8)		
Pain: Week 24 (n=116,92)	-4.1 (± 29.35)	2.1 (± 27.78)		
Pain: Week 32 (n=69,60)	-1 (± 27.17)	3.9 (± 32.49)		
Pain: Week 40 (n=48,31)	1.6 (± 31.82)	1.3 (± 28.96)		
Pain: Week 48 (n=30,19)	-0.8 (± 30.82)	-0.4 (± 25.23)		
Pain: Week 56 (n=26,16)	-4.2 (± 22.88)	0.5 (± 33.95)		
Dyspnoea: Week 8 (n=339,313)	0.7 (± 25.02)	5.8 (± 24.59)		
Dyspnoea: Week 16 (n=180,158)	-1.1 (± 26.34)	4.6 (± 26.99)		
Dyspnoea: Week 24 (n=116,92)	-2 (± 25.65)	1.4 (± 20.47)		
Dyspnoea: Week 32 (n=68,60)	0 (± 24.77)	8.6 (± 29.67)		
Dyspnoea: Week 40 (n=48,30)	2.4 (± 27.93)	5 (± 25.95)		
Dyspnoea: Week 48 (n=30,19)	-5.6 (± 26.38)	-0.9 (± 19.62)		
Dyspnoea: Week 56 (n=26,14)	-7.1 (± 18.36)	-1.2 (± 22.13)		
Insomnia: Week 8 (n=338,315)	-1.5 (± 28.1)	3.3 (± 30.28)		
Insomnia: Week 16 (n=180,160)	-1.4 (± 24.4)	2.1 (± 27.2)		

Insomnia: Week 24 (n=116,92)	-2.7 (± 31.77)	1.3 (± 26.41)		
Insomnia: Week 32 (n=68,59)	1.5 (± 34.04)	2.5 (± 30.14)		
Insomnia: Week 40 (n=48,30)	0 (± 31.51)	4.4 (± 22.71)		
Insomnia: Week 48 (n=30,19)	2.8 (± 28.05)	0.9 (± 34.01)		
Insomnia: Week 56 (n=26,16)	-1.3 (± 35.57)	-1 (± 27.53)		
Appetite loss: Week 8 (n=340,314)	11.6 (± 32.03)	4 (± 30.26)		
Appetite loss: Week 16 (n=180,159)	9.4 (± 32.16)	-2.1 (± 29.75)		
Appetite loss: Week 24 (n=116,92)	4.6 (± 36.55)	-1.6 (± 30.57)		
Appetite loss: Week 32 (n=69,60)	8.9 (± 35.42)	0 (± 32.04)		
Appetite loss: Week 40 (n=48,31)	6.9 (± 38.57)	5.4 (± 38.58)		
Appetite loss: Week 48 (n=30,18)	2.2 (± 34.67)	13 (± 45.93)		
Appetite loss: Week 56 (n=26,16)	14.7 (± 35.38)	1 (± 39.19)		
Constipation: Week 8 (n=337,310)	2.1 (± 29.95)	6.7 (± 27.81)		
Constipation: Week 16 (n=181,158)	0.2 (± 31.03)	3.1 (± 30.96)		
Constipation: Week 24 (n=116,90)	0.6 (± 29.65)	-2 (± 28.14)		
Constipation: Week 32 (n=69,59)	4.6 (± 29.83)	0.3 (± 26.53)		
Constipation: Week 40 (n=48,31)	1 (± 28.44)	-3.2 (± 29.32)		
Constipation: Week 48 (n=29,19)	-0.6 (± 31.65)	7 (± 33.48)		
Constipation: Week 56 (n=26,15)	1.9 (± 34.42)	-4.4 (± 35.34)		
Diarrhoea: Week 8 (n=339,311)	10.2 (± 27.98)	1.8 (± 16.87)		
Diarrhoea: Week 16 (n=181,158)	10.8 (± 26.97)	3.4 (± 19.07)		
Diarrhoea: Week 24 (n=114,89)	9.4 (± 26.43)	2.4 (± 16.39)		
Diarrhoea: Week 32 (n=69,59)	9.2 (± 21.3)	0.8 (± 17.07)		
Diarrhoea: Week 40 (n=48,30)	8.3 (± 23.06)	7.8 (± 27.93)		
Diarrhoea: Week 48 (n=29,19)	12.1 (± 22.23)	0 (± 17.57)		
Diarrhoea: Week 56 (n=26,15)	4.5 (± 14.57)	6.7 (± 31.37)		
Financial difficulties: Week 8 (n=339,312)	-0.7 (± 22.87)	0.6 (± 22.42)		
Financial difficulties: Week 16 (n=181,159)	0.8 (± 23.26)	1 (± 22.48)		
Financial difficulties: Week 24 (n=115,90)	1 (± 21.09)	4.6 (± 28.38)		
Financial difficulties: Week 32 (n=69,59)	1.2 (± 20.28)	10.2 (± 26.81)		
Financial difficulties: Week 40 (n=48,30)	4.2 (± 21.61)	-1.7 (± 19.74)		
Financial difficulties: Week 48 (n=29,19)	0 (± 22.27)	3.5 (± 18.9)		
Financial difficulties: Week 56 (n=26,15)	-1.9 (± 21.25)	5.6 (± 25.72)		

Statistical analyses

Statistical analysis title	Analysis for HRQoL QLQ-C30 Change from Baseline
Statistical analysis description:	
Global health status/QoL: change from baseline to last assessment (Week 56)	
Comparison groups	NKTR-102 v TPC drugs

Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[2]
P-value	= 0.635
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.65
upper limit	4.33

Notes:

[2] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-C30 Change from Baseline

Statistical analysis description:

Physical functioning: change from baseline to last assessment (Week 56)

Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	= 0.1656
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	5.14

Notes:

[3] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-C30 Change from Baseline

Statistical analysis description:

Role functioning: change from baseline to last assessment (Week 56)

Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[4]
P-value	= 0.8356
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	4.82

Notes:

[4] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-C30 Change from Baseline

Statistical analysis description:

Emotional functioning: change from baseline to last assessment (Week 56)

Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[5]
P-value	= 0.7727
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.88
upper limit	3.88

Notes:

[5] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-C30 Change from Baseline

Statistical analysis description:

Cognitive functioning: change from baseline to last assessment (Week 56)

Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[6]
P-value	= 0.7446
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.56
upper limit	3.59

Notes:

[6] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-C30 Change from Baseline

Statistical analysis description:	
Social functioning: change from baseline to last assessment (Week 56)	
Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[7]
P-value	= 0.9169
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	4.45

Notes:

[7] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-C30 Change from Baseline
Statistical analysis description:	
Fatigue: change from baseline to last assessment (Week 56)	
Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[8]
P-value	= 0.9731
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.66
upper limit	3.79

Notes:

[8] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-C30 Change from Baseline
Statistical analysis description:	
Nausea and vomiting: change from baseline to last assessment (Week 56)	
Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[9]
P-value	< 0.0001
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	7.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.88
upper limit	10.67

Notes:

[9] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-C30 Change from Baseline

Statistical analysis description:

Pain: change from baseline to last assessment (Week 56)

Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[10]
P-value	= 0.1252
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.59
upper limit	0.93

Notes:

[10] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-C30 Change from Baseline

Statistical analysis description:

Dyspnoea: change from baseline to last assessment (Week 56)

Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[11]
P-value	= 0.1717
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.83
upper limit	1.22

Notes:

[11] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-C30 Change from Baseline

Statistical analysis description:	
Insomnia: change from baseline to last assessment (Week 56)	
Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[12]
P-value	= 0.5513
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.95
upper limit	3.18

Notes:

[12] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-C30 Change from Baseline
Statistical analysis description:	
Appetite loss: change from baseline to last assessment (Week 56)	
Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[13]
P-value	= 0.0009
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	8.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.57
upper limit	13.72

Notes:

[13] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-C30 Change from Baseline
Statistical analysis description:	
Constipation: change from baseline to last assessment (Week 56)	
Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[14]
P-value	= 0.2337
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	-2.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.35
upper limit	1.8

Notes:

[14] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-C30 Change from Baseline

Statistical analysis description:

Diarrhoea: change from baseline to last assessment (Week 56)

Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[15]
P-value	< 0.0001
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	10.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.6
upper limit	13.98

Notes:

[15] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-C30 Change from Baseline

Statistical analysis description:

Financial difficulties: change from baseline to last assessment (Week 56)

Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[16]
P-value	= 0.99
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.74
upper limit	3.69

Notes:

[16] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Secondary: Quality of Life Questionnaire-breast cancer-specific module (BR23) score value: ITT Population

End point title	Quality of Life Questionnaire-breast cancer-specific module (BR23) score value: ITT Population

End point description:

The QLQ-BR23 incorporates 5 multi-item scales to assess systemic therapy side effects, arm symptoms, breast symptoms, body image and sexual functioning, and 3 single items to assess sexual enjoyment, upset by hair loss and future perspective. n=number of subjects who completed each individual scale.

End point type	Secondary

End point timeframe:

Baseline

End point values	NKTR-102	TPC drugs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	429	423		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Body image (n=421,408)	69.5 (± 28.94)	69.9 (± 27.91)		
Sexual functioning (n=410,388)	14.1 (± 19.24)	13.3 (± 18.91)		
Sexual enjoyment (n=184,166)	36.1 (± 29.25)	34.2 (± 30.77)		
Future perspective (n=421,406)	38.7 (± 30.53)	36.1 (± 29)		
Systemic therapy side effects (n=423,408)	21.9 (± 16.37)	22.3 (± 15.15)		
Breast symptoms (n=423,408)	15.3 (± 21.55)	15.8 (± 20.79)		
Arm symptoms (n=423,409)	20.8 (± 23.4)	22.2 (± 22.75)		
Upset by hair loss (n=244,225)	33.2 (± 34.15)	30.5 (± 33.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: BR23 score change over time: ITT Population

End point title	BR23 score change over time: ITT Population

End point description:

The QLQ-BR23 incorporates 5 multi-item scales to assess systemic therapy side effects, arm symptoms, breast symptoms, body image and sexual functioning, and 3 single items assess sexual enjoyment, upset by hair loss and future perspective. n=number of subjects who completed each individual scale. Because the number of patients that completed the HRQoL questionnaires decreased to below 10% of the population beyond 32 weeks, meaningful HRQoL analyses were not reliable after Week 32.

End point type	Secondary

End point timeframe:

Change from Baseline to End-of -Treatment

End point values	NKTR-102	TPC drugs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	429	423		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Body image: Week 8 (n=342,310)	-0.8 (± 21.99)	-2.2 (± 20.49)		
Body image: Week 16 (n=178,162)	-0.8 (± 24.31)	-2.3 (± 20.91)		
Body image: Week 24 (n=113,96)	0.8 (± 23.58)	-4.7 (± 20.97)		
Body image: Week 32 (n=68,62)	-1.2 (± 26.27)	-0.3 (± 22.23)		
Body image: Week 40 (n=48,30)	3.3 (± 22.63)	-2.4 (± 20.98)		
Body image: Week 48 (n=29,20)	-0.3 (± 25.47)	-1.1 (± 28.93)		
Body image: Week 56 (n=27,16)	3.9 (± 25.53)	-10.2 (± 26.61)		
Sexual functioning: Week 8 (n=320,286)	-0.8 (± 16.07)	-2.2 (± 16.26)		
Sexual functioning: Week 16 (n=166,143)	0.1 (± 16.67)	-0.8 (± 17.28)		
Sexual functioning: Week 24 (n=100,82)	-2.8 (± 16.72)	-1.4 (± 15.7)		
Sexual functioning: Week 32 (n=61,57)	-2.2 (± 19.12)	-0.7 (± 12.82)		
Sexual functioning: Week 40 (n=43,25)	-5.4 (± 16.66)	2.7 (± 16.27)		
Sexual functioning: Week 48 (n=26,16)	-9.6 (± 19.68)	1.6 (± 15.88)		
Sexual functioning: Week 56 (n=25,15)	-5.3 (± 17.33)	1.7 (± 13.06)		
Sexual enjoyment: Week 8 (n=96,68)	2.6 (± 19.84)	-4.2 (± 23.64)		
Sexual enjoyment: Week 16 (n=51,33)	-0.3 (± 18.41)	-8.6 (± 21.7)		
Sexual enjoyment: Week 24 (n=27,19)	1.9 (± 29.72)	-3.5 (± 28.1)		
Sexual enjoyment: Week 32 (n=17,13)	2 (± 23.48)	-2.6 (± 20.24)		
Sexual enjoyment: Week 40 (n=12,7)	-15.3 (± 29.69)	7.1 (± 13.11)		
Sexual enjoyment: Week 48 (n=6,5)	-27.8 (± 25.09)	6.7 (± 14.91)		
Sexual enjoyment: Week 56 (n=7,4)	-9.5 (± 16.27)	0 (± 0)		
Future perspective: Week 8 (n=342,309)	3.5 (± 28.3)	1.5 (± 27.21)		
Future perspective: Week 16 (n=180,162)	6.9 (± 27.17)	3.6 (± 29.18)		
Future perspective: Week 24 (n=113,94)	9.3 (± 31.1)	6.6 (± 29.55)		
Future perspective: Week 32 (n=66,61)	6.1 (± 30.19)	4.4 (± 35.86)		
Future perspective: Week 40 (n=49,30)	7.1 (± 28.05)	13.3 (± 37.75)		
Future perspective: Week 48 (n=29,19)	9.2 (± 27.31)	6.1 (± 35.66)		
Future perspective: Week 56 (n=25,16)	16 (± 28.25)	-3.1 (± 45.22)		
Systemic therapy side effects: Week 8 (n=345,312)	2.3 (± 13.74)	7.9 (± 16.03)		
Systemic therapy side effects: Week 16 (n=181,162)	3 (± 14.95)	9.1 (± 17.7)		
Systemic therapy side effects: Week 24 (n=115,96)	2.2 (± 15.55)	6.9 (± 17.39)		
Systemic therapy side effects: Week 32 (n=69,62)	3.5 (± 13.5)	7.3 (± 18.01)		
Systemic therapy side effects: Week 40 (n=49,30)	3.2 (± 16.62)	10.1 (± 18.33)		
Systemic therapy side effects: Week 48 (n=30,20)	0.3 (± 11.74)	6.4 (± 15.68)		
Systemic therapy side effects: Week 56 (n=27,16)	-1.1 (± 11.06)	6.8 (± 21.84)		
Breast symptoms: Week 8 (n=342,310)	-1.7 (± 15.21)	-0.2 (± 13.82)		

Breast symptoms: Week 16 (n=177,159)	-3.5 (± 14.6)	0.1 (± 14.64)		
Breast symptoms: Week 24 (n=115,97)	-4.8 (± 10.52)	-1.1 (± 13.48)		
Breast symptoms: Week 32 (n=69,60)	-2.5 (± 14.26)	-2.8 (± 13.63)		
Breast symptoms: Week 40 (n=48,30)	-1.9 (± 14.59)	-0.2 (± 11.02)		
Breast symptoms: Week 48 (n=29,20)	-2.7 (± 12.16)	0 (± 13.79)		
Breast symptoms: Week 56 (n=26,16)	-3.4 (± 13.28)	2.5 (± 12.15)		
Arm symptoms: Week 8 (n=342,312)	-3 (± 16.72)	-0.9 (± 15.01)		
Arm symptoms: Week 16 (n=178,159)	-5.1 (± 17.24)	1.1 (± 18.24)		
Arm symptoms: Week 24 (n=115,97)	-4.9 (± 20.06)	-0.3 (± 19.56)		
Arm symptoms: Week 32 (n=69,60)	-4.4 (± 18.39)	-0.5 (± 19.03)		
Arm symptoms: Week 40 (n=48,30)	-6 (± 21.86)	5.2 (± 18.39)		
Arm symptoms: Week 48 (n=29,20)	-5.6 (± 20.89)	-1.4 (± 12.98)		
Arm symptoms: Week 56 (n=26,16)	-5.6 (± 19.44)	-1.4 (± 19.51)		
Upset by hair loss: Week 8 (n=102,122)	-4.7 (± 32.28)	0.1 (± 28.63)		
Upset by hair loss: Week 16 (n=54,58)	8.3 (± 33.61)	2.9 (± 31.24)		
Upset by hair loss: Week 24 (n=37,38)	6.8 (± 35.02)	3.5 (± 30.3)		
Upset by hair loss: Week 32 (n=17,22)	6.9 (± 31.76)	-2.3 (± 29.68)		
Upset by hair loss: Week 40 (n=20,14)	-4.2 (± 30.05)	20.2 (± 29.37)		
Upset by hair loss: Week 48 (n=7,10)	-16.7 (± 31.91)	21.7 (± 36.89)		
Upset by hair loss: Week 56 (n=8,5)	-14.6 (± 30.13)	16.7 (± 44.1)		

Statistical analyses

Statistical analysis title	Analysis for HRQoL QLQ-BR23 Change from Baseline

Statistical analysis description:

Body image: change from baseline to last assessment (Week 56)

Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[17]
P-value	= 0.5833
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.42
upper limit	4.29

Notes:

[17] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-BR23 Change from Baseline

Statistical analysis description:

Sexual functioning: change from baseline to last assessment (Week 56)

Comparison groups	NKTR-102 v TPC drugs

Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[18]
P-value	= 0.3098
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.24
upper limit	3.9

Notes:

[18] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-BR23 Change from Baseline

Statistical analysis description:

Future perspective: change from baseline to last assessment (Week 56)

Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[19]
P-value	= 0.6264
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.39
upper limit	5.63

Notes:

[19] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-BR23 Change from Baseline

Statistical analysis description:

Systemic therapy side effects: change from baseline to last assessment (Week 56)

Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[20]
P-value	= 0.0003
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	-4.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.11
upper limit	-2.1

Notes:

[20] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-BR23 Change from Baseline

Statistical analysis description:

Breast symptoms: change from baseline to last assessment (Week 56)

Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[21]
P-value	= 0.2473
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.84
upper limit	0.99

Notes:

[21] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-BR23 Change from Baseline

Statistical analysis description:

Arm symptoms: change from baseline to last assessment (Week 56)

Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[22]
P-value	= 0.0333
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.54
upper limit	-0.23

Notes:

[22] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-BR23 Change from Baseline

Statistical analysis description:	
Upset by hair loss: change from baseline to last assessment (Week 56)	
Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[23]
P-value	= 0.2575
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.2
upper limit	3.28

Notes:

[23] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Statistical analysis title	Analysis for HRQoL QLQ-BR23 Change from Baseline
Statistical analysis description:	
Sexual enjoyment: change from baseline to last assessment (Week 56)	
Comparison groups	NKTR-102 v TPC drugs
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	equivalence[24]
P-value	= 0.1072
Method	F-test
Parameter estimate	Mean difference (final values)
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.22
upper limit	12.34

Notes:

[24] - Analysis of variance with change from baseline in linear transformed score at the last visit as the dependent variable and treatment arm, geographic region, prior use of eribulin, and receptor status as fixed effects.

Secondary: Population Mean ± Standard Deviation (SD) Area Under the Concentration-Time Curve (AUC) for NKTR-102 and Metabolites after Multiple Administration of 145 mg/m^2 NKTR-102

End point title	Population Mean ± Standard Deviation (SD) Area Under the Concentration-Time Curve (AUC) for NKTR-102 and Metabolites after Multiple Administration of 145 mg/m^2 NKTR-102[25]

End point description:

Plasma concentrations of NKTR-102 and its major metabolites irinotecan, SN38, SN38G, and APC were measured using validated analytical methods. The population pharmacokinetic (PK) model-derived mean AUC values were computed by integration from t = 0 (start of first dose) to 21 days after the last dose. Integration was implemented using a separate compartment defined as the amount of drug or metabolite in the central compartment divided by the model-estimated volume of distribution.

End point type	Secondary

End point timeframe:

From the first dose up to 21 days after the last dose.

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants from "NKTR-102" treatment arm were planned to be analysed for this end point.

End point values	NKTR-102			
Subject group type	Reporting group			
Number of subjects analysed	95			
Units: µg·h/mL				
arithmetic mean (standard deviation)				
NKTR-102	4619 (± 4874)			
Irinotecan	18.8 (± 22.1)			
SN38	5.32 (± 6.74)			
SN38G	40.6 (± 39.2)			
APC	4 (± 5.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Population Mean ± SD Maximum Plasma Concentration (Cmax) for NKTR-102 and Metabolites after Multiple Administration of 145 mg/m^2 NKTR-102

End point title	Population Mean ± SD Maximum Plasma Concentration (Cmax) for NKTR-102 and Metabolites after Multiple Administration of 145 mg/m^2 NKTR-102[26]

End point description:

Plasma concentrations of NKTR-102 and its major metabolites irinotecan, SN38, SN38G, and APC were measured using validated analytical methods. The population PK model-derived mean Cmax values were computed by integration from t = 0 (start of first dose) to 21 days after the last dose. Integration was implemented using a separate compartment defined as the amount of drug or metabolite in the central compartment divided by the model-estimated volume of distribution.

End point type	Secondary

End point timeframe:

From the first dose up to 21 days after the last dose.

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants from "NKTR-102" treatment arm were planned to be analysed for this end point.

End point values	NKTR-102			
Subject group type	Reporting group			
Number of subjects analysed	95			
Units: ng/mL				
arithmetic mean (standard deviation)				
NKTR-102	62701 (± 14576)			
Irinotecan	138 (± 61.8)			

SN38	4.45 (± 1.82)			
SN38G	47.7 (± 43.1)			
APC	7.3 (± 6.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Population Mean ± SD Elimination Half-life (t½) for NKTR-102 after Multiple Administration of 145 mg/m^2 NKTR-102

End point title	Population Mean ± SD Elimination Half-life (t½) for NKTR-102 after Multiple Administration of 145 mg/m^2 NKTR-102[27]

End point description:

Plasma concentrations of NKTR-102 and its major metabolites irinotecan, SN38, SN38G, and APC were measured using validated analytical methods. The population PK model-derived mean t½ values were computed by integration from t = 0 (start of first dose) to 21 days after the last dose. Integration was implemented using a separate compartment defined as the amount of drug or metabolite in the central compartment divided by the model-estimated volume of distribution. The t½ of all analytes was primarily driven by NKTR-102. Thus, the NKTR-102 t½ of 37 days also applies to all NKTR-102 metabolites.

End point type	Secondary

End point timeframe:

From the first dose up to 21 days after the last dose.

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants from "NKTR-102" treatment arm were planned to be analysed for this end point.

End point values	NKTR-102			
Subject group type	Reporting group			
Number of subjects analysed	95			
Units: days				
arithmetic mean (standard deviation)	36.8 (± 1.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR): Efficacy Evaluable Population

End point title	Objective Response Rate (ORR): Efficacy Evaluable Population

End point description:

ORR was defined as the proportion of subjects with a complete response (CR) or a partial response (PR), assessed by the investigator based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 The analyses were performed for subjects in the efficacy evaluable population who had measurable disease as determined by the investigator at baseline.

End point type	Secondary

End point timeframe:

Every 8 weeks (± 7 days) from date of randomisation until protocol-defined disease progression.

End point values	NKTR-102	TPC drugs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	358		
Units: Percentage of subjects				
number (confidence interval 95%)	16.4 (12.7 to 20.7)	17 (13.3 to 21.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and serious adverse events were reported from the time the patient received the first dose of study drug through the End-of-Treatment Visit (i.e., 30 ± 3 days after the last dose of study drug).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	NKTR-102

Reporting group description:

NKTR-102 for injection was administered as an IV infusion over 90 ± 15 minutes, on Day 1 of each 21-day cycle) at a dose level of 145 mg/m^2.

Reporting group title	TPC drugs

Reporting group description:

The TPC drugs were administered in 21- or 28-day treatment cycles, depending on the institutional guidelines for the specific drug. The dosage and administration of the TPC drugs followed the institutional guidelines provided for each agent, with the exception of: Eribulin, which was administered in accordance with its local country Summary of Product Characteristics (SmPC) or Prescribing Information OR initially administered at no less than 1.4 mg/m^2 on Days 1 and 8 every 21 days; Ixabepilone, which was initially administered at 40 mg/m2 on Day 1 every 21 days, then per institutional guidelines.

Serious adverse events	NKTR-102	TPC drugs	
Total subjects affected by serious adverse events			
subjects affected / exposed	128 / 425 (30.12%)	129 / 406 (31.77%)	
number of deaths (all causes)	323	322	
number of deaths resulting from adverse events	3	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	6 / 425 (1.41%)	10 / 406 (2.46%)	
occurrences causally related to treatment / all	0 / 6	0 / 11	
deaths causally related to treatment / all	0 / 3	0 / 3	
Metastases to meninges			
subjects affected / exposed	2 / 425 (0.47%)	4 / 406 (0.99%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain			

subjects affected / exposed	2 / 425 (0.47%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	1 / 425 (0.24%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to spine			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Ovarian cancer			

subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 425 (0.71%)	5 / 406 (1.23%)	
occurrences causally related to treatment / all	0 / 3	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 425 (0.71%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 3	2 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
Asthenia			
subjects affected / exposed	1 / 425 (0.24%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chest pain			
subjects affected / exposed	0 / 425 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 425 (0.47%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 425 (0.24%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 425 (0.24%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 425 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 425 (0.24%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malaise			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Pelvic pain			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	15 / 425 (3.53%)	18 / 406 (4.43%)	
occurrences causally related to treatment / all	0 / 21	0 / 21	
deaths causally related to treatment / all	0 / 2	0 / 4	
Dyspnoea			
subjects affected / exposed	2 / 425 (0.47%)	7 / 406 (1.72%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 425 (0.24%)	5 / 406 (1.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 6	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pulmonary embolism			
subjects affected / exposed	4 / 425 (0.94%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 425 (0.47%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 425 (0.24%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung infiltration			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 425 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood bilirubin increased			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium test positive			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress fracture			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 425 (0.24%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrest			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			

subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	3 / 425 (0.71%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 425 (0.24%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 425 (0.47%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			

subjects affected / exposed	3 / 425 (0.71%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholinergic syndrome			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysgraphia			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gliosis			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			

subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal chord compression			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 425 (0.47%)	6 / 406 (1.48%)	
occurrences causally related to treatment / all	2 / 3	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 425 (0.47%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 425 (0.47%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic thrombocytopenic purpura			

subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microangiopathic haemolytic anaemia			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein occlusion			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	17 / 425 (4.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	18 / 18	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	10 / 425 (2.35%)	6 / 406 (1.48%)	
occurrences causally related to treatment / all	5 / 10	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ascites			
subjects affected / exposed	4 / 425 (0.94%)	5 / 406 (1.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	4 / 425 (0.94%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	2 / 4	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 425 (0.47%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 425 (0.24%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 425 (0.24%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 425 (0.24%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	2 / 425 (0.47%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 425 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal discomfort			

subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colonic obstruction			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal hypomotility			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileitis			

subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	3 / 425 (0.71%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Bile duct obstruction			
subjects affected / exposed	1 / 425 (0.24%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatomegaly			

subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	3 / 425 (0.71%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Renal failure			
subjects affected / exposed	2 / 425 (0.47%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 425 (0.24%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 425 (0.24%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 425 (0.24%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 425 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal osteoarthritis			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 425 (0.94%)	4 / 406 (0.99%)	
occurrences causally related to treatment / all	1 / 4	0 / 4	
deaths causally related to treatment / all	1 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 425 (0.94%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	1 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 425 (0.24%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 425 (0.24%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 425 (0.24%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 425 (0.47%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	2 / 425 (0.47%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	1 / 425 (0.24%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 425 (0.24%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 425 (0.24%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 425 (0.24%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Urosepsis			
subjects affected / exposed	0 / 425 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 425 (0.24%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess intestinal			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute haemorrhagic conjunctivitis			

subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast infection			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Moraxella infection			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			

subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Oral herpes			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	8 / 425 (1.88%)	6 / 406 (1.48%)	
occurrences causally related to treatment / all	7 / 8	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 2	
Hypercalcaemia			

subjects affected / exposed	2 / 425 (0.47%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 425 (0.47%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 425 (0.24%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyponatraemia			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 425 (0.24%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 425 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	NKTR-102	TPC drugs	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	417 / 425 (98.12%)	404 / 406 (99.51%)	
Investigations			
Weight decreased			
subjects affected / exposed	57 / 425 (13.41%)	24 / 406 (5.91%)	
occurrences (all)	65	25	
Neutrophil count decreased			
subjects affected / exposed	26 / 425 (6.12%)	50 / 406 (12.32%)	
occurrences (all)	41	126	
Aspartate aminotransferase increased			
subjects affected / exposed	23 / 425 (5.41%)	29 / 406 (7.14%)	
occurrences (all)	24	31	
Nervous system disorders			
Dizziness			
subjects affected / exposed	55 / 425 (12.94%)	41 / 406 (10.10%)	
occurrences (all)	75	51	
Dysgeusia			
subjects affected / exposed	34 / 425 (8.00%)	28 / 406 (6.90%)	
occurrences (all)	41	44	
Neuropathy peripheral			
subjects affected / exposed	9 / 425 (2.12%)	50 / 406 (12.32%)	
occurrences (all)	9	62	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	145 / 425 (34.12%)	130 / 406 (32.02%)	
occurrences (all)	241	163	
Asthenia			
subjects affected / exposed	91 / 425 (21.41%)	114 / 406 (28.08%)	
occurrences (all)	142	170	
Pyrexia			
subjects affected / exposed	30 / 425 (7.06%)	63 / 406 (15.52%)	
occurrences (all)	39	98	
Oedema peripheral			

subjects affected / exposed	20 / 425 (4.71%)	42 / 406 (10.34%)	
occurrences (all)	22	49	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	92 / 425 (21.65%)	126 / 406 (31.03%)	
occurrences (all)	174	244	
Anaemia			
subjects affected / exposed	64 / 425 (15.06%)	82 / 406 (20.20%)	
occurrences (all)	83	105	
Eye disorders			
Vision blurred			
subjects affected / exposed	68 / 425 (16.00%)	12 / 406 (2.96%)	
occurrences (all)	161	13	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	255 / 425 (60.00%)	155 / 406 (38.18%)	
occurrences (all)	479	249	
Diarrhoea			
subjects affected / exposed	277 / 425 (65.18%)	79 / 406 (19.46%)	
occurrences (all)	1202	128	
Vomiting			
subjects affected / exposed	172 / 425 (40.47%)	72 / 406 (17.73%)	
occurrences (all)	342	109	
Constipation			
subjects affected / exposed	112 / 425 (26.35%)	126 / 406 (31.03%)	
occurrences (all)	167	152	
Abdominal pain			
subjects affected / exposed	89 / 425 (20.94%)	47 / 406 (11.58%)	
occurrences (all)	147	52	
Abdominal pain upper			
subjects affected / exposed	56 / 425 (13.18%)	37 / 406 (9.11%)	
occurrences (all)	71	45	
Dyspepsia			
subjects affected / exposed	34 / 425 (8.00%)	32 / 406 (7.88%)	
occurrences (all)	45	50	
Stomatitis			

subjects affected / exposed	17 / 425 (4.00%)	34 / 406 (8.37%)	
occurrences (all)	23	43	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	58 / 425 (13.65%)	70 / 406 (17.24%)	
occurrences (all)	68	87	
Cough			
subjects affected / exposed	59 / 425 (13.88%)	52 / 406 (12.81%)	
occurrences (all)	64	55	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	44 / 425 (10.35%)	95 / 406 (23.40%)	
occurrences (all)	49	102	
Rash			
subjects affected / exposed	23 / 425 (5.41%)	24 / 406 (5.91%)	
occurrences (all)	28	28	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	29 / 425 (6.82%)	33 / 406 (8.13%)	
occurrences (all)	45	35	
Anxiety			
subjects affected / exposed	20 / 425 (4.71%)	22 / 406 (5.42%)	
occurrences (all)	26	23	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	26 / 425 (6.12%)	59 / 406 (14.53%)	
occurrences (all)	30	89	
Back pain			
subjects affected / exposed	39 / 425 (9.18%)	39 / 406 (9.61%)	
occurrences (all)	45	41	
Arthralgia			
subjects affected / exposed	29 / 425 (6.82%)	42 / 406 (10.34%)	
occurrences (all)	35	55	
Pain in extremity			
subjects affected / exposed	27 / 425 (6.35%)	35 / 406 (8.62%)	
occurrences (all)	32	43	

Bone pain			
subjects affected / exposed	17 / 425 (4.00%)	35 / 406 (8.62%)	
occurrences (all)	20	38	
Musculoskeletal pain			
subjects affected / exposed	25 / 425 (5.88%)	26 / 406 (6.40%)	
occurrences (all)	28	29	
Muscle spasms			
subjects affected / exposed	29 / 425 (6.82%)	16 / 406 (3.94%)	
occurrences (all)	60	16	
Musculoskeletal chest pain			
subjects affected / exposed	16 / 425 (3.76%)	26 / 406 (6.40%)	
occurrences (all)	16	31	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	26 / 425 (6.12%)	26 / 406 (6.40%)	
occurrences (all)	27	28	
Upper respiratory tract infection			
subjects affected / exposed	15 / 425 (3.53%)	27 / 406 (6.65%)	
occurrences (all)	18	32	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	130 / 425 (30.59%)	98 / 406 (24.14%)	
occurrences (all)	169	116	
Hypokalaemia			
subjects affected / exposed	39 / 425 (9.18%)	37 / 406 (9.11%)	
occurrences (all)	54	39	
Dehydration			
subjects affected / exposed	34 / 425 (8.00%)	19 / 406 (4.68%)	
occurrences (all)	39	25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2012	The major changes made to the protocol were: 1. The requirement for the Xeloda® brand of capecitabine was amended to permit patients to receive generic capecitabine where available and approved by the local country Competent Authority. 2. Clarify that investigators selected a TPC that was approved by the Local Competent Authority and commercially available in that country. 3. A tissue acquisition protocol sub-study was added to the main study. 4. Clarification of Eligibility Criteria. 5. The United States Adopted Name for NKTR-102 (etirinotecan pegol) was added to the protocol. References to United States Pharmacopeia (USP) for diluents were removed. Documentation of the lot number of NKTR-102 administered to each patient was required in the electronic case report form. Shelf-life increased from 30 to 36 months based on additional stability data. Changes were also made to Dosing Modification, Supportive Care and Prohibited Medications. 6. For the TPC, nab-albumin paclitaxel was changed to nab-paclitaxel throughout the protocol, information regarding diluents (locally sourced) was added and references regarding USP were removed. 7. Modifications were made to the following procedures: the definition of human epidermal growth factor receptor 2-positive disease was removed; added that patients received a Patient Information Card at time of consent; updated the instructions for bone scans; updated the text for laboratory tests for screening and treatment; updated the timing of PK sample collection; updated text relating to biomarkers, brain imaging, positron emission tomography–computed tomography, health-related quality of life and Health Economics questionnaires, and Safety.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported