Clinical trial results:
An Open-label, Multicenter, Extension Study of NKTR-102 in Subjects Previously Enrolled in NKTR-102 Studies

Summary

EudraCT number	2011-002797-23
Trial protocol	BE
Global end of trial date	23 August 2017

Results information

Result version number	v1 (current)
This version publication date	19 December 2018
First version publication date	19 December 2018

Trial information

Trial identification

Sponsor protocol code	11-PIR-09

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01457118
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Nektar Therapeutics
Sponsor organisation address	455 Mission Bay Boulevard South, San Francisco, CA, United States, 94158
Public contact	Nektar Therapeutics, Nektar Therapeutics, 001 855-482-8676, studyinquiry@nektar.com
Scientific contact	Nektar Therapeutics, Nektar Therapeutics, 001 855-482-8676, 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	23 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To provide access to NKTR-102 treatment to subjects previously enrolled in a NKTR-102 study, who were without signs of disease progression since receiving NKTR-102. The study evaluated the safety of continued exposure to NKTR-102, observed disease and survival status and evaluated the efficacy of NKTR-102 in subjects with advanced or metastatic solid tumours.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 September 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	United States: 24
Country: Number of subjects enrolled	Belgium: 2
Worldwide total number of subjects	27
EEA total number of subjects	2

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)	22

From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 8 study sites in 3 countries.

Pre-assignment

Screening details:

Subjects, who previously received NKTR-102 in a clinical trial and were without signs of disease progression since receiving NKTR-102, were enrolled in this study. Subjects were to receive repeated cycles of NKTR-102 as long as there was evidence of disease control in the judgment of the Investigator.

Period 1

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

Arms

Arm title	NKTR-102

Arm description:

Subjects received NKTR-102 on Day 1 of each 21-day treatment cycle.

Arm type	Experimental
Investigational medicinal product name	NKTR-102
Investigational medicinal product code	
Other name	etirinotecan pegol
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

A 90-minute intravenous (IV) infusion of NKTR-102 on Day 1 of each 21-day treatment cycle.

Number of subjects in period 1	NKTR-102
Started	27
Completed	0
Not completed	27
Physician decision	2
Death	19
Study terminated by sponsor	4
Withdrawal by subject	2

Baseline characteristics

Reporting groups	
Reporting group title	NKTR-102
Reporting group description:	
Subjects received NKTR-102 on Day 1 of each 21-day treatment cycle.	

Reporting group values	NKTR-102	Total	
Number of subjects	27	27	
Age categorical Units: Subjects			

Age continuous			
Safety Population included all subjects who received at least one dose of study treatment.			
Units: years arithmetic mean standard deviation	 56.0 ± 10.01	 -	
Gender categorical			
Safety Population included all subjects who received at least one dose of study treatment.			
Units: Subjects			
Female	17	17	
Male	10	10	

End points

End points reporting groups

Reporting group title	NKTR-102
Reporting group description:	
Subjects received NKTR-102 on Day 1 of each 21-day treatment cycle.	

Primary: Percentage of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point title	Percentage of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)[1]

End point description:

An adverse event was defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. TEAE was any event not present before exposure to the study drug or any event already present that worsened in either intensity or frequency after exposure to the study drug. A serious adverse event is any event that fulfilled at least one of the following criteria: fatal, life-threatening, required in-patient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was medically significant or required intervention to prevent any of the other outcomes listed here. Safety Population included all subjects who received at least one dose of study treatment.

End point type	Primary

End point timeframe:

From baseline up to approximately 5 years and 11 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data were planned to be reported for the endpoint.

End point values	NKTR-102			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: percentage of subjects				
number (not applicable)				
TEAE	100.0			
TESAE	25.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate by Investigator

End point title	Best Overall Response Rate by Investigator

End point description:

Data on best overall response for complete response (CR) or partial response (PR) were collected as determined by the investigator according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1). Tumour measurements were not required; only an overall assessment of response or progression by the Investigator was required. CR: disappearance of all target lesions. PR: At least a 30% decrease in all target lesions. The best overall response rate was calculated as number of subjects with response/number of subjects who had measurable lesions. Safety Population included all subjects

who received at least one dose of study treatment. Overall number of subjects analysed is the number of subjects with data available for analysis at the given time-point.

End point type	Secondary

End point timeframe:

From baseline up to approximately 5 years and 11 months

End point values	NKTR-102			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: percentage of subjects				
number (confidence interval 95%)	0 (0.0 to 14.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline up to approximately 5 years and 11 months	
Adverse event reporting additional description:	
Safety Population included all subjects who received at least one dose of study treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	NKTR-102
Reporting group description:	
Subjects received NKTR-102 on Day 1 of each 21-day treatment cycle.	

Serious adverse events	NKTR-102		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 27 (25.93%)		
number of deaths (all causes)	19		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Appendix cancer			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cancer pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes simplex encephalitis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Peritonitis bacterial			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	NKTR-102		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 27 (96.30%)		
Investigations			
Weight decreased			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	5		
Neutrophil count decreased			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	4		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
White blood cell count decreased			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	5		
Neutropenia			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 27 (29.63%)		
occurrences (all)	8		
Oedema peripheral			

subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	 4 / 27 (14.81%) 4		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all)	 14 / 27 (51.85%) 20 6 / 27 (22.22%) 7 6 / 27 (22.22%) 8 5 / 27 (18.52%) 5 4 / 27 (14.81%) 4 2 / 27 (7.41%) 2		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	 3 / 27 (11.11%) 4		
Skin and subcutaneous tissue disorders Decubitus ulcer subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 2 / 27 (7.41%) 2 2 / 27 (7.41%) 2		

Rash subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all)	 3 / 27 (11.11%) 3 2 / 27 (7.41%) 2		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypoalbuminaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypoglycaemia subjects affected / exposed occurrences (all) Hyponatraemia subjects affected / exposed occurrences (all)	 6 / 27 (22.22%) 6 4 / 27 (14.81%) 4 3 / 27 (11.11%) 7 2 / 27 (7.41%) 4 2 / 27 (7.41%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2013	The protocol was modified to enable enrolment of subjects from varied study designs. Clarified that a subject may receive treatment for approximately 2 years, but the study could last about 5 years due to follow-up for survival status after treatment with NKTR-102 stops. The section on dose modifications and delays was updated to accommodate doses other than 145 mg/m^2. Updated sections on adverse events to properly describe the reporting of AEs that could occur to subjects during the transition from their original protocol to this extension study. Updated the description of use of anti-diarrhoeal therapy to include the most current advice regarding prophylactic use of atropine for cholinergic symptoms and recommend the use of loperamide to treat diarrhoea. Incorporated a section on use of growth factor support and transfusions to describe their allowable use in greater detail. Updated the permitted and prohibited treatments to include more detail and provide current requirements. Updated text regarding pregnancy and use of adequate birth control. Provided a more comprehensive list of CYP3A4 inhibitors and inducers that are prohibited during the study.
25 September 2013	Included a study objective and endpoint to evaluate the efficacy of NKTR-102 in subjects with advanced or metastatic solid tumours. Added Eastern Cooperative Oncology Group (ECOG) performance status at Screening and each treatment visit, and added physical examination, vital signs, and ECOG performance status assessments to the End-of-Treatment visit.
14 January 2016	Added +/- 4 week window to the long-term follow-up visit schedule. Updated the exclusion criterion which stated that subjects who would be scheduled to receive a dose < 70 mg/m^2 would be excluded, to allow subjects with moderate or severe hepatic impairment (treated with a dose of 50 mg/m^2). Clarified the method for calculating body surface area (BSA): to be determined before the start of each cycle, based on baseline height and most recent weight. Included dose reduction guidelines for subjects entering the study at a starting dose of 50 mg/m^2. Included additional recommendations for NKTR-102 dose modifications following toxicities. Updated advisements on late-onset diarrhoea to align with information in other clinical study protocols currently using NKTR-102. Removed dose schedule from analysis of maximum intensity and frequency of AEs: AEs summarized by treatment (dose level).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported