Clinical Study Report Synopsis

Drug Substance	NKTR-118 (also known as naloxegol)
Study Code	D3820C00006
Edition Number	1
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EudraCT Number	2011-001985-16

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of NKTR-118 in Relieving Opioid-Induced Constipation (OIC) in Patients with Cancer-Related Pain

Study dates: First subject enrolled: 29 June 2011
Last subject last visit: 20 September 2012

Phase of development: Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Introduction

This was a Phase III, multi-center placebo-controlled, double-blind study of NKTR-118 in patients with cancer-related pain and opioid-induced constipation (OIC).

Study centres

Approximately 672 patients were planned to be enrolled to obtain 336 randomized patients. The study was originally to be conducted at approximately 150 centers in the United States and 15 other countries. [redacted]

Due to recruitment challenges, enrolment to this study was stopped early and no new patients had been screened as of 20 April 2012. Fourteen patients were randomized across the 3 treatment groups (fewer than 5% of the planned number), thus, there was an insufficient number of patients to perform the protocol specified formal statistical analyses. Thus, a Synopsis-format Clinical Study Report (CSR) was prepared to report study data.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objectives	Outcome variables	Type	Part of study
Primary	**Primary**		
To compare the efficacy of NKTR-118 12.5 and 25 mg with placebo in the treatment of patients who have OIC in pain related to malignancy in a 4-week double-blind study (Part A).	Response (responder/non-responder) to study drug, where a responder is defined as having at least 3 RFBMs per week during the 4-week placebo-controlled treatment period, with at least 1 RFBM per week increase over baseline for at least 3 out of 4 weeks.	Efficacy	A
Secondary	**Secondary**		
To compare NKTR-118 12.5 mg and 25 mg with placebo on the daily signs and symptoms associated with OIC (degree of straining, sensation of incomplete evacuation, and stool consistency), symptoms of constipation, and overall quality of life over a 4-week double-blind study (Part A).	Part A and Part B: Change from baseline in RFBMs/week.	Efficacy	A/B
To characterize the maintenance of effect of NKTR-118 over a 12-week extension (Part B).	Part A and Part B: Mean number of days per week with at least 1 RFBM.		A/B
	Part A: Time (in hours) to first post-dose RFBM.		A

Objectives	Outcome variables	Type	Part of study
	Part A: Change from baseline in the degree of straining associated with RFBMs during the 4-week placebo-controlled treatment period.		A
	Part A: Change from baseline in BSS during the 4-week placebo-controlled treatment period.		A
	Part A: Percentage of days with complete evacuation during the 4 week placebo controlled treatment period.		A
	Part B: Duration of response during the 12-week extension period.		B
	Part A and B: Change from baseline in PAC-SYM total score and each domain score.		A/B
	Part A and B: Change from baseline in PAC-QOL total score and each domain score.		A/B
Safety	**Safety**		
To assess the safety and tolerability of NKTR-118 12.5 and 25 mg, when used for the treatment of OIC.	AEs (ie, incidence, nature, and intensity of AEs, treatment-related AEs, SAEs, AEs leading to discontinuation, and AEs of special interest).	Safety	A/B
	Change from baseline in the mean daily opioid dose during the 4-week treatment period (Part A) and the 12-week extension period (Part B).		A/B
	Change from baseline in NRS pain score during the 4 week treatment period (Part A) and the 12-week extension period (Part B).		A/B
	Observed values and change from baseline in composite score in mHS for the evaluation of centrally-mediated opioid withdrawal symptoms at Weeks 1 and 4 (Part A), as well as Weeks 1, 4, and 12 (Part B).		A/B
	Changes from baseline in vital signs and physical examination.		A/B
	Changes from baseline in laboratory assessments (ie, chemistry, hematology, and urinalysis).		A/B
	Change from baseline in ECG parameters.		A/B
Exploratory	**Exploratory**		
To characterize the PK of NKTR-118 and the covariate effect in the targeted disease population, explore the NKTR-118 exposure-response relationship, collect and store DNA for future exploratory research, and to assess patient health status index.	Population PK modelling.	PK[a], PK/PD	A

Objectives	Outcome variables	Type	Part of study
	Exposure/ response modelling.	PK[a], PK/PD	A
	Data on the EQ-5D questionnaire for Week 4.	Health Economic	A
To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to NKTR-118.	DNA extracted from the optional blood samples may be used to explore relationships between genetic variability and NKTR-118 PK/PD, safety, tolerability, response, and OIC.	Pgx	A

[a] Not reported in this synopsis-format CSR.
[b] A responder is defined as having at least 3 rescue-free bowel movements (RFBMs) per week during the 4-week placebo-controlled treatment period, with at least 1 RFBM per week increase over baseline for at least 3 out of 4 weeks.

AE adverse event; BSS Bristol Stool Scale; CSR clinical study report; DNA deoxyribonucleic acid; ECG electrocardiogram; EQ-5D European Quality of Life Visual Analogue Scale and 5 dimensions; mHS Modified Himmelsbach scale; NRS Numeric Rating Scale; OIC opioid-induced constipation; PAC-QOL Patient Assessment of Constipation Quality of Life; PAC-SYM Patient Assessment of Constipation Symptoms; PD pharmacodynamic; Pgx pharmacogenetic; PK pharmacokinetic; RFBM rescue-free bowel movement; SAE serious adverse event.

Note: An independent external Data Safety Monitoring Board (DSMB) was formed to monitor patient safety and independent adjudication committees (ACs) were assembled to adjudicate bowel-perforation and CV events of interest. These independent committees were never formally convened due to the small number of enrolled patients.

Note: The US DEA classified NKTR-118 as a Schedule II compound in 2010. Accordingly, following this decision an abuse liability monitoring plan (ALMP) was implemented in the new and ongoing NKTR-118 studies. Investigators were trained to report a variety of medication use irregularities using a Suspected Abuse Liability Event (SALE) form.

Study design

This was a Phase III, multi-center, placebo-controlled, double-blind study of NKTR-118 in patients with cancer-related pain and OIC. The study consisted of 2 Parts: Part A and Part B. Part A was a double-blind, randomized, placebo-controlled, parallel group study to evaluate the efficacy and safety of NKTR-118 12.5 mg and 25 mg in the treatment of OIC in cancer patients with pain related to malignancy over a 4-week period. Malignancy-related pain included pain directly related to a tumor or pain resulting from the direct treatment of a tumor (eg, neuropathic pain as a result of tumor resection, mucositis, or peripheral neuropathic pain as a result of chemotherapy or radiation therapy).

All patients were to have the opportunity to transition from Part A (the double-blind portion of the study) to Part B (the active treatment extension), provided they met the relevant criteria. Part B was to be an active treatment extension to assess the safety and tolerability of NKTR-118 in the treatment of OIC in cancer-related pain during an additional 12 weeks of treatment.

Patients who were on active treatment were to be allocated to the same NKTR-118 treatment/dose through the Interactive Voice Response System (IVRS). Patients who were on placebo were to be allocated to receive NKTR-118 25 mg through the IVRS. Part B of the study was to remain blinded.

Target subject population and sample size

Patients (≥18 years or older) with a histologically or cytologically confirmed neoplasm and with a life expectancy of ≥3 months who were receiving a stable maintenance opioid regimen (total daily dose of ≥30 mg of oral morphine, or equianalgesic amount[s] of 1 or more other opioid therapies) for a minimum of 4 weeks prior to screening for cancer-related pain with no anticipated change in opioid dose requirement as a result of disease progression over the proposed 4-week study period were eligible to be randomized. The target population must have reported a history of <3 rescue-free bowel movements (RFBMs)/week and at least 1 OIC associated symptom at screening and have a confirmed diagnosis of OIC. A RFBM was defined as a bowel movement (BM) without rescue laxatives in the previous 24 hours. Confirmed OIC was defined as documented <3 RFBMs/week on average over the 2-week OIC confirmation period. Patients with uneven distribution of RFBMs across the 2-week OIC confirmation period (0 RFBMs in 1 week with ≥4 RFBMs in the other week) were excluded. In addition to the RFBM frequency criterion, patients must have reported ≥1 of the following symptoms in at least 25% of the BMs recorded in the electronic diary (eDiary) during the OIC confirmation period: Bristol Stool Scale (BSS) stool type 1 or 2; moderate, severe, or very severe straining; incomplete BM. Patients who had 0 BMs in the 7 days prior to randomization were not randomized.

Investigational product and comparator(s): dosage and mode of administration and batch numbers

NKTR-118 12.5 or 25 mg tablets, or matching placebo, administered once daily. Individual batch numbers and further information are included in the CSR appendix.

Duration of treatment

Part A: Approximately 8 weeks, consisting of an initial screening period (14 days), a 2-week OIC confirmation period, during which the diagnosis of OIC and stability of opioid regimen were confirmed, and a 4-week treatment period.

Should the patient have discontinued study drug in Part A, or completed Part A, but chose not to continue into Part B, a follow-up visit occurred 2 weeks after the last dose of study drug. In addition to this, these patients also received a follow-up telephone call approximately 18 weeks after randomization to collect vital status data.

Part B: Approximately 14 weeks, consisting of a 12-week treatment period and a follow-up visit 2 weeks after the last dose of study drug.

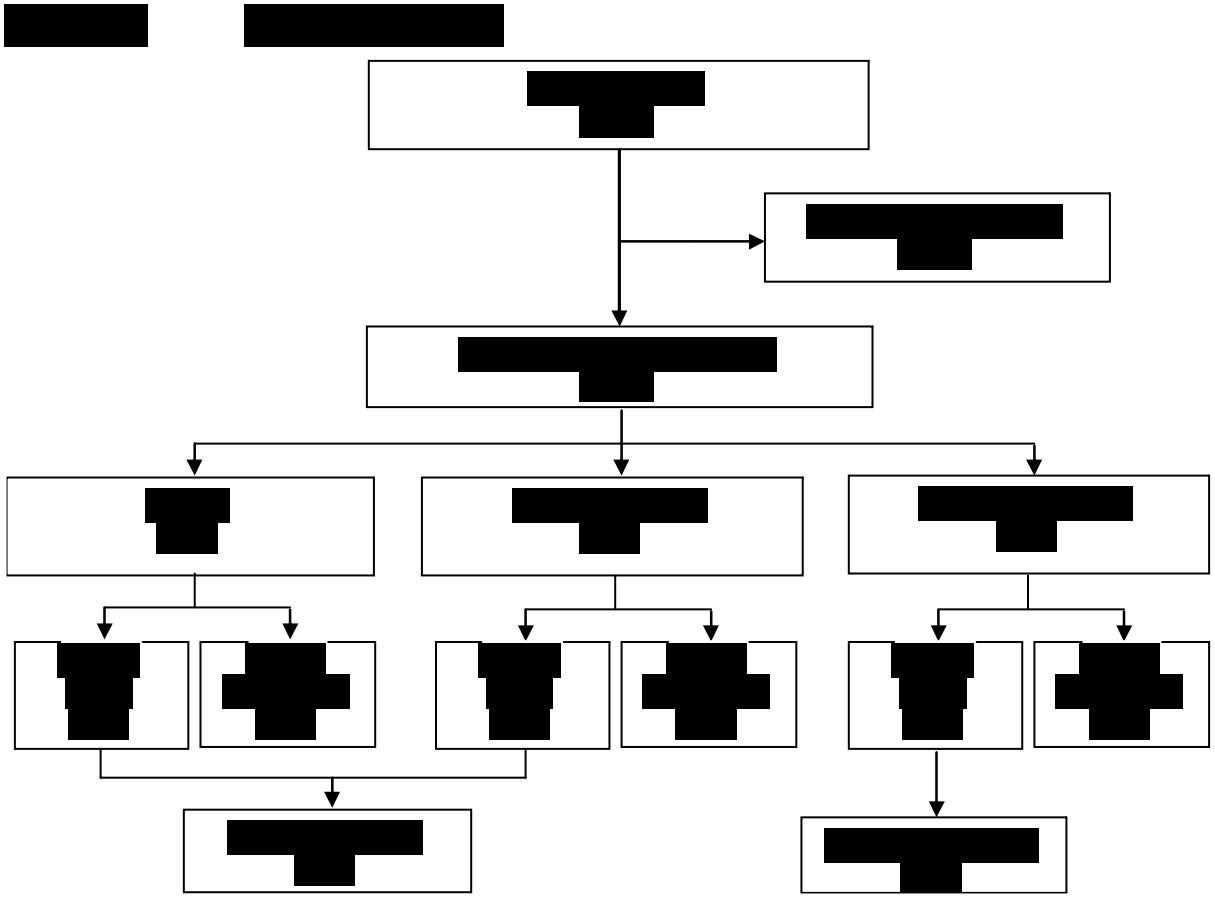
Statistical methods

Because the number of patients randomized was insufficient to adequately address the study objectives, no formal statistical analyses were conducted and only a subset of the planned data presentations are provided.

The efficacy analysis set was the Intent-to-Treat (ITT) population, defined as all randomized patients participating in the relevant study part (Part A and/or Part B). Efficacy data were listed according to randomized treatment. The safety analysis set included all randomized patients who received at least 1 dose of study drug. The safety analysis set was used to assess safety and tolerability variables. Patients were analyzed according to the treatment they received.

Subject population

A summary of patient disposition is presented below:



A total of 44 patients were enrolled in the study and of these, 14 were randomized (5 to NKTR-118 25 mg, 5 to NKTR-118 12.5 mg, and 4 to placebo). All 14 randomized patients received treatment and went on to complete Part A of the study. Of the 14 completers of Part A, 9 patients (64.3%) continued into the single-blind extension Part B of the study (3 [60.0%] in the NKTR-118 25 mg group, 3 [60.0%] in the NKTR-118 12.5 mg group, and

3 [75.0%] in the placebo group). [redacted]

Patient demographic characteristics are summarized as follows:

Table 2 Demographic characteristics (Safety set)

Demographic characteristics	Placebo - NKTR-118 25 mg (N = 4)	NKTR-118 12.5 mg - NKTR-118 12.5 mg (N = 5)	NKTR-118 25 mg - NKTR-118 25 mg (N = 5)	Total (N = 14)
Age (years) [a]				
n	4	5	5	14
Mean	52.5	55.8	53.8	54.1
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

ITT intent to treat; SD standard deviation.
[a] Age is calculated as the rounded down integer value in years of [(Date of consent – Date of Birth)/365.25].
Note: The percentages are based on the number of ITT patients in each treatment group with non-missing data for the parameter.
Note: The 'Total' column summarizes across all treatment groups.
Source: Table 11.1.2.1.

Patient cancer history:

Of the 14 patients enrolled in the study, the types of cancer identified at study entry (past and present) included uterine cancer, throat cancer, breast cancer or breast cancer metastatic, vulval cancer, hepatic neoplasm malignant, pelvic cancer, renal cancer, cervix carcinoma, uterine cancer, multiple myeloma, and myelodysplastic syndrome, lip and/or oral cavity cancer, bone neoplasm malignant, and metastases to lymph nodes.

Concomitant medications:

All patients took at least 1 concomitant medication during the treatment period. [redacted]

Maintenance opioids:

[redacted] At baseline during the OIC confirmation period, the daily maintenance opioid dose ranged from morphine equivalence of 45.0-1440.0 mg/day.

Summary of efficacy results

Of the 14 patients in the study, 9 experienced an average of ≥3 RFBMs/week and a ≥1 RFBM increase to Week 4 over baseline, indicating response per the definition specified in the statistical analysis plan. Three out of 5 patients in the NKTR-118 25 mg group, 4 out of 5 patients in the NKTR-118 12.5 mg group, and 2 out of 4 patients in the placebo group demonstrated response.

Summary of safety results

In the 14 patients evaluated in this study, NKTR-118 at doses of 12.5 and 25 mg was generally safe and well-tolerated over 12 weeks of treatment for OIC:

- No deaths, other serious AEs (SAEs), or discontinuations due to AEs occurred during the study.
- During Part A of the study, 2 patients (40.0%) in the NKTR-118 25 mg group, 3 patients (60.0%) in the NKTR-118 12.5 mg group, and 2 patients (50.0%) in the placebo group reported AEs.
  - Overall, the most common AEs during Part A were from the system organ class (SOC) of gastrointestinal (GI) disorders [redacted]
  - Treatment-emergent AEs in the GI SOC during Part A included the preferred terms of haematochezia and nausea in the NKTR-118 12.5 mg group and nausea in the NKTR-118 25 mg group.

- During Part B of the study, [redacted] in the NKTR-118 25 mg group and 1 patient [redacted] in the NKTR-118 12.5 mg group reported AEs. No AE preferred term was observed in more than a single patient during Part B.

- No AEs met the criteria to be sent for adjudication.

[redacted]

[redacted]

[redacted]