AstraZeneca

Clinical Study Report Synopsis

Drug Substance	NKTR-118 (also known as naloxegol)
Study Code	D3820C00007
Edition Number	1

A Randomized, Double-Blind, Placebo-Controlled 12-Week Extension Study to Assess the Safety and Tolerability of NKTR-118 in Patients with Non-Cancer-Related Pain and Opioid-Induced Constipation (OIC)

Study dates:	First subject rolled into D3820C00007 extension: 07 July 2011 Last subject last visit in D3820C00007 extension: 13 September 2012
Phase of development:	Therapeutic confirmatory (III)

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

Study centers

This study was conducted in 52 study centers in the United States (US).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To compare NKTR-118 12.5 mg and 25 mg with placebo regarding long-term safety and tolerability in the treatment of OIC using descriptive statistics.	• Adverse events (ie, incidence, nature, and intensity of AEs, treatment-related AEs, SAEs, AEs leading to discontinuation, and AEs of special interest) • Change from baseline in the mean daily opioid dose for Weeks 1 to 4 and 1 to 12 • Mean bisacodyl dose per week for Weeks 4 and 12 • Change from baseline in the mean NRS pain score for Weeks 4, 8, and 12 • Observed values and change from baseline in composite score in mHS for the evaluation of centrally mediated opioid withdrawal at Week 12 • Changes in physical examination and changes in vital signs • Changes in laboratory assessments (ie, chemistry, hematology, and urinalysis • Changes in ECGs • Occurrence of suicidal behavior/suicidal ideation throughout the study based on the C-SSRS	Safety
Secondary	**Secondary**	
To assess the impact of NKTR-118 12.5 mg and 25 mg on symptoms of constipation and quality of life.	• Change from baseline in PAC-SYM total score and each domain score for Weeks 4, 12, and 14 • Change from baseline in PAC-QOL total score and each domain score for Weeks 4, 12, and 14	Efficacy
Exploratory	**Exploratory**	
To assess patient health status index and healthcare resource utilization.	• Data on the EQ-5D questionnaire at enrolment, Weeks 4, 12, and 14. • Data on OIC Healthcare Resource Utilization captured at the site for economic modeling purposes	Health Economic

Table S1 Primary and secondary objectives and outcome variables

Note: For the purpose of data summaries, in order to place the results into context with prior exposure on study drug, summaries of data by protocol scheduled time point were labelled according to time relative to first dose in Study D3820C00004, eg, Week 0 of the current study is reported as Week 12.
AE adverse event; C-SSRS Columbia-Suicide Severity Rating Scale; ECG electrocardiogram; EQ-5D European Quality of Life; 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; SAE Serious adverse event.

Study design

This was a 12-week extension of the Phase III, multicenter, double-blind, randomized, placebo-controlled, parallel group 12 week study D3820C00004 to evaluate the safety and tolerability of NKTR-118 12.5 mg and 25 mg with placebo in the treatment of OIC in patients with non-cancer-related pain. Patients continued on their randomized dose from the D3820C00004 study.

Target subject population and sample size

Patients who successfully completed the D3820C00004 study were eligible to participate.

No formal sample size calculation was performed for this long-term safety study. The sample size was determined by the number of patients from the previous study D3820C00004 who enrolled.

Investigational product and comparator(s): dosage, 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 clinical study report appendix.

Duration of treatment

The duration of treatment was 12 weeks.

Statistical methods

Results were summarized using frequency and percentages for categorical data and n, mean, standard deviation, median, minimum, maximum for continuous data.

This was a general evaluation of safety and tolerability; therefore, no statistical testing was conducted. Differences between NKTR-118 12.5 mg and 25 mg and placebo with respect to the evaluation of long-term safety, tolerability, and efficacy were assessed using descriptive statistics.

The safety analysis set was used to assess the safety and tolerability. All randomized patients who received at least 1 dose of study drug in the current study were included in the safety analysis set, with the exception of patients who were found to have randomized multiple times within the program at different centers.

The efficacy analyses were based on a modified Intent-to-Treat analysis set that included all randomized patients who received at least 1 dose of study drug in the current study and had at least 1 post-baseline efficacy measurement (Patient Assessment of Constipation Symptoms [PAC-SYM] or Patient Assessment of Constipation Quality of Life [PAC-QOL]).

Subject population

A total of 302 patients rolled over from Study D3820C00004 and continued in the double-blind treatment period at 52 study centers in the US.

Of the 302 patients enrolled in the current study, 297 (98.3%) received treatment, 245 (81.1%) completed the study, and 46 (15.2%) received treatment and subsequently discontinued the study. The treatment groups were generally balanced in terms of discontinuations: 15 (15.2%), 17 (17.5%), and 14 (13.2%) patients in the NKTR-118 25 mg, 12.5 mg, and placebo groups, respectively, discontinued the study. The most common reasons for study withdrawal were patient decision (20 patients; 6.6%) and adverse events (AEs) (11 patients; 3.6%).

A total of 6 additional patients completed the study, but had previously or concurrently participated in the NKTR-118 program at another study center and were excluded from the safety analysis set.

Overall, there were no notable imbalances across the treatment groups in terms of patient characteristics that could have a potential influence on the results and their interpretation. Treatment groups were generally balanced across analysis sets with respect to: disposition; protocol deviations; demographic and baseline characteristics (where baseline characteristics were assessed prior to randomization in Study D3820C00004); prior and concomitant medications, including the pattern of laxative classes taken prior to study entry, satisfaction with laxative classes, and the pattern of related severity of symptoms; rescue medication (ie, bisacodyl) use; and treatment compliance. All enrolled patients were from the US.

There was a notable imbalance across the treatment groups in the number of patients with ongoing GI events from the preceding study (Study D3820C00004), with no patients in the placebo group reported with any ongoing GI events compared with 13 (13.3%) and 8 (8.4%) patients in the NKTR-118 25 mg and 12.5 mg groups, respectively. The most common ongoing GI event was abdominal pain, which was reported more frequently in the NKTR-118 25 mg group.

Summary of efficacy results

At baseline (Study D3820C00004), the mean PAC-SYM domain scores across all 3 treatment groups indicated that patients in the study were most affected by symptoms in the stool domain (moderate to severe) and impacted to a lesser extent (mild to moderate) by symptoms in the abdominal and rectal domains. The improvement in mean domain scores of the PAC-SYM observed in the 12-week confirmatory study (Study D3820C00004) was maintained in this extension study.

At entry into this extension study, patients in each treatment group had a change in total PAC-SYM scores of -0.8 points compared to baseline (improvement of symptoms). These improvements were maintained at the final on-treatment assessment in each group (mean changes from baseline of -0.8, -0.9, and -0.9 in the placebo, 12.5 mg, and 25 mg NKTR-118 groups, respectively). This maintenance of improvement was also seen in the individual domains of PAC-SYM.

At entry into this extension study, each treatment group had similar changes in the mean total PAC-QOL domain scores (improvement in quality of life) compared to baseline (-0.8, -1.0, -0.8 in the placebo, 12.5 mg, and 25 mg groups, respectively). These improvements were maintained at the final on-treatment assessment (-0.8, -1.0 and -0.9 in the placebo, 12.5 mg, and 25 mg groups, respectively). This maintenance of improvement was also seen in the individual domains of PAC-QOL.

Summary of safety results

The following table presents the number and percentage of patients who had at least 1 AE in any category during the randomized treatment and follow-up periods.

Table S2 Number (%) of patients who had at least 1 AE in any category during the treatment period or post-treatment follow-up (Safety analysis set)

AE Category	Number (%) patients [a]		
	Placebo (N = 100)	NKTR-118 12.5 mg (N = 94)	NKTR-118 25 mg (N = 97)
Any AE	33 (33.0)	32 (34.0)	40 (41.2)
Any AE with outcome = death	0	1 (1.1)	0
Any SAE (including events with outcome = death)	5 (5.0)	6 (6.4)	6 (6.2)
Any AE leading to permanent discontinuation of IP	3 (3.0)	4 (4.3)	4 (4.1)

[a] The percentages are based on the number of patients in the Safety analysis set in each treatment group.
Note: AEs that started on or after the first dose of IP in the current D3820C00007 study are included.
Note: Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
Note: AEs leading to discontinuation of IP only include those events that included permanent discontinuation of IP.
AE adverse event; IP investigational product; SAE serious AE.
Source: Table 11.3.2.1.1.

In this 12-week extension study of OIC patients who had previously participated in a 12-week confirmatory study of NKTR-118 versus placebo, NKTR-118, at doses of 12.5 mg and 25 mg, was generally safe and well-tolerated. Most AEs were mild or moderate in intensity and the most common treatment-emergent AEs (TEAEs) in the NKTR-118 treatment groups were arthralgia and diarrhoea, which occurred at a higher frequency in the NKTR-118 treatment groups compared with placebo.

One death was reported (myocardial ischaemia) during the follow-up period in the NKTR-118 12.5 mg group, considered by the investigator as not related to IP. There was no notable imbalance observed for the type or frequency of SAEs across treatment groups and the incidence of discontinuations of IP due to an AE (DAEs) was low and no notable imbalance was observed for the type or frequency of DAEs across treatment groups.

There was no notable imbalance across treatment groups with respect to the incidence of cardiovascular (CV) AEs. There was 1 CV event adjudicated as MACE in the NKTR-118 12.5 mg group (adjudicated as 'Cardiovascular death') and 1 other CV event of interest in the NKTR-118 25 mg group (adjudicated as 'Heart failure requiring hospitalization'). Neither event was considered by the investigator to be related to IP. There was no notable imbalance in AEs related to changes in blood pressure and there were no AEs adjudicated as bowel perforation events.

NKTR-118 was not associated with clinically important changes in centrally mediated opioid withdrawal signs as assessed by the mHS, and there were no clinically important changes for average pain intensity scores in any treatment group, as measured by the NRS assessed over the last 7 days prior to a scheduled visit.

Analysis of mean daily opioid dose showed no clinically important increase or decrease in any of the treatment groups.

NKTR-118 was not associated with clinically important changes in laboratory, vital signs, ECG, or physical examination variables, including the immediate post-dose time period. Furthermore, there were no clinically important imbalances for the NKTR-118 treatment groups compared to placebo in numbers of outliers for systolic blood pressure, diastolic blood pressure, heart rate, or QTcF at any time point throughout the study.

There was no notable imbalance across the treatment groups with respect to suicidal behavior or ideation as assessed by C-SSRS and AEs.