AstraZeneca

Clinical Study Report Synopsis

Drug Substance	NKTR-118 (also known as naloxegol)
Study Code	D3820C00004
Edition Number	1
Date	17 May 2013

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

Study dates: First subject enrolled: 14 March 2011
Last subject last visit: 16 August 2012

Phase of development: Therapeutic confirmatory (III)

[redacted]

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

Study centers

Of the 138 study centers selected for this study, 115 screened at least 1 patient and 98 randomized patients into the study. This study was conducted in the following countries: Australia, Germany, Slovakia, and 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 the efficacy of NKTR-118 12.5 mg and 25 mg with placebo in the treatment of patients who have OIC.	Response (responder/non-responder) to study drug during Weeks 1 to 12[a].	Efficacy
Key Secondary	**Key Secondary**	
To compare the efficacy of NKTR-118 12.5 mg and 25 mg with placebo in the treatment of patients who have OIC.	Response (responder/non-responder) to study drug in the LIR subgroup during Weeks 1 to 12[a].	Efficacy
	Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours.	
	Mean number of days per week with at least 1 SBM[b] during Weeks 1 to 12.	
Other Secondary	**Other Secondary**	
To compare the efficacy of NKTR-118 12.5 mg and 25 mg with placebo in the treatment of patients who have OIC.	Response (responder/non-responder) to study drug during Weeks 1 to 4[c].	Efficacy
	Response (responder/non-responder) to study drug in the LIR subgroup during Weeks 1 to 4[c].	
	Change from baseline in number of SBMs/week for Weeks 1 to 4 and 1 to 12.	
	Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours in the LIR subgroup.	
	Response within the first 12 hours of treatment.	
	Mean number of days per week with at least 1 SBM[b] for Weeks 1 to 4.	
To compare NKTR-118 12.5 mg and 25 mg with placebo on the daily signs and symptoms associated with OIC (straining, sensation of incomplete evacuation, and stool consistency), symptoms of constipation, and quality of life.	Change from baseline in the mean degree of straining for Weeks 1 to 4 and 1 to 12.	Efficacy
	Change from baseline in the mean stool consistency (BSS) for Weeks 1 to 4 and 1 to 12.	

Objectives	Outcome variables	Type
	Percentage of days with CSBM for Weeks 1 to 4 and 1 to 12.	
	Mean bisacodyl dose per week for Weeks 1 to 4 and 1 to 12.	
	Change from baseline in PAC-SYM total score and each domain score for Weeks 2, 4, 8, and 12.	
	Change from baseline in PAC-QOL total score and each domain score for Weeks 4 and 12.	
Safety	**Safety**	
To assess the safety and tolerability of NKTR-118 12.5 mg and 25 mg, when used for the treatment of OIC.	Adverse events (ie, incidence, nature, and intensity of AEs, treatment-related AEs, SAEs, AEs leading to discontinuation, and AEs of special interest).	Safety
	Change from baseline in the mean daily opioid dose for Weeks 1 to 4 and 1 to 12.	
	Change from baseline in the mean NRS pain score for Weeks 1 to 4 and 1 to 12.	
	Observed values and change from baseline in composite score in mHS for the evaluation of centrally mediated opioid withdrawal symptoms 2 hours after first dose of study drug, and at Weeks 1, 4, and 12.	
	Changes in vital signs, weight and BMI, and changes in physical examination.	
	Changes in laboratory assessments (ie, chemistry, hematology, and urinalysis).	
	Changes in ECGs.	
	Occurrence of suicidal behaviour/suicidal ideation throughout the study based on the C-SSRS.	
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, assess patient health status index and healthcare resource utilization, and assess patients' willingness to take the study drug again.	Population PK modelling work.	PK[d], PK/PD
	Exposure/ response modelling work.	PK[d], PK/PD
	Data on the EQ-5D questionnaire for Weeks 4 and 12.	Health Economic
	Data on OIC healthcare resource utilization captured at the site for economic modelling purposes.	

Objectives	Outcome variables	Type
	Willingness to Take Drug Again questionnaire for Week 12.	Health Economic
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 responder was defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 9 out of 12 weeks, and at least 3 out of the last 4 weeks.

[b] SBM was defined as a BM without the use of rescue laxatives (bisacodyl or enema) administered in the previous 24 hours. For the endpoint "mean number of days per week with at least 1 SBM", calculation of the endpoint was clarified to ensure that a day when a patient experienced excessive SBMs (more than 3 SBMs) would not contribute as a day with at least 1 SBM in the analysis. This ensured that patients regularly experiencing excessive BMs on treatment, an undesirable treatment effect, would not bias the analysis towards demonstrating a difference between treatment groups.

[c] A responder was defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 3 out of the first 4 weeks.

[d] Reported separately from this CSR.

AE adverse event; BM bowel movement; BMI body mass index; BSS Bristol Stool Scale; CSBM complete spontaneous bowel movement; CSR clinical study report; C-SSRS Columbia-Suicide Severity Rating Scale; DNA deoxyribonucleic acid; ECG electrocardiogram; EQ-5D European Quality of Life Visual Analogue Scale and 5 dimensions; LIR laxative inadequate responder/response; 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; SAE serious adverse event; SBM spontaneous bowel movement.

Study design

This was a Phase III, multi-center, double-blind, randomized, placebo-controlled, parallel group study of 2 doses of NKTR-118 (25 mg and 12.5 mg) and placebo. The study duration was up to 18 weeks, consisting of an initial screening period lasting up to 2 weeks, a 2-week opioid-induced constipation (OIC) confirmation period, during which the diagnosis of OIC and stability of the opioid regimen were confirmed, a 12-week treatment period, and a follow-up visit 2 weeks after the last dose of study drug. Patients who successfully completed the 12-week treatment period were eligible to participate in a separate safety extension study; patients continuing into the safety extension study did not participate in the 2-week follow-up period of the current study.

Target subject population and sample size

Adult patients who were receiving a stable maintenance opioid regimen (total daily dose of 30 to 1000 mg of oral morphine, or equianalgesic amount[s] of 1 or more other opioid therapies for a minimum of 4 weeks) for non-cancer-related pain and who reported a history of <3 spontaneous bowel movements (SBMs)/week and at least 1 OIC associated symptom at screening and had a confirmed diagnosis of OIC were eligible to be randomized.

Confirmed OIC was defined as: documented <3 SBMs/week on average over the 2-week OIC confirmation period. Patients with uneven distribution of SBMs across the 2-week OIC confirmation period (0 SBMs in 1 week with ≥4 SBMs in the other week) were to be excluded. In addition to the SBM frequency criterion, patients must have reported ≥1 of the following symptoms in at least 25% of the bowel movements (BMs) recorded in the electronic diary during the OIC confirmation period: Bristol Stool Scale stool type 1 or 2; moderate, severe, or very severe straining; incomplete BM. Patients who had 0 BMs over the 2-week OIC confirmation period were not randomized.

In addition, a minimum of 50% of patients were to meet the following criteria for being laxative inadequate responders (LIR): Patient must have been taking 1 laxative class for a minimum of 4 days prior to the screening visit and report moderate, severe, or very severe symptoms in at least 1 of the 4 stool symptom domains to qualify for assessment of LIR.

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 (CSR) appendix.

Duration of treatment

The duration of treatment was 12 weeks.

Statistical methods

To provide an adequate power to detect a treatment difference in the LIR subgroup (assuming LIR is 50% of the total study population), it was recommended that 210 patients per group (total 630 patients for 3 treatment groups) be randomized to the study.

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

Treatment comparisons were made between each active treatment group (NKTR-118 12.5 mg and 25 mg) vs placebo for all data analyzed.

The primary endpoint, response over 12 weeks, was analyzed using Cochran-Mantel-Haenszel (CMH) tests stratified by response to laxatives at baseline (LIR, laxative adequate responder [LAR], laxative unknown responder [LUR]). The treatment effect was further characterized by the relative risk (RR, NKTR-118/placebo) with associated 2-sided 95% confidence intervals (CIs).

The following were categorized as key secondary endpoints and analyzed as indicated:

1. Comparison of the response rate of Weeks 1 to 12 of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo in the LIR subgroup. Difference between treatment groups in response rate was analyzed using Chi-Square tests.

The treatment effect was characterized by the RR (NKTR-118 group/placebo) with associated 2-sided 95% CIs.

2. Treatment comparisons of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo, for the time to first laxation without laxative use in the previous 24 hours were analyzed using log rank tests stratified by response to laxatives at baseline (LIR, LAR, LUR).

3. Comparison of the mean number of days per week with at least 1 SBM during the 12 weeks of treatment of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. Differences between treatment groups were analyzed using a mixed model for repeated measures. The model included factors for treatment, baseline laxative response status, time (Weeks 1 through 12 as a categorical variable), mean baseline value and treatment-by-time interaction as fixed effects, and center as a random effect. Descriptive statistics for the mean number of days per week with at least 1 SBM over Weeks 1 to 12 were also presented by treatment group.

To control the overall type I error rate to be ≤ 0.05 for the multiple comparisons in the primary and the key secondary endpoints, a Multiple Testing Procedure with Bonferroni-Holm over groups, and fixed-sequence within groups was applied, with the endpoints tested in the order indicated above. This multiplicity adjustment method follows the general results described by Bretz (Bretz et al 2009) and by Burman (Burman et al 2009).

Endpoints for daily symptoms, Patient Assessment of Constipation Symptoms (PAC-SYM), Patient Assessment of Constipation Quality of Life (PAC-QOL), morphine equivalent dose, and Numeric Rating Scale (NRS) pain score, were analyzed using a mixed model repeated measures approach in a similar manner to that described above.

Subject population

A total of 1750 patients were enrolled in the study and of these, 652 patients completed the OIC confirmation period, were randomized, and entered the double-blind treatment period. Of the randomized patients, 99.5% received treatment, 80.4% completed the study (defined as completing Visit 8 [Week 12] for patients who continued into the safety extension study, or completing Visit 9 [Week 14] for patients who did not continue into the safety extension study), and 17.5% received treatment and subsequently discontinued the study. Of the 652 randomized patients, 297 (45.6%) who were included in the intent-to-treat (ITT) analysis set completed the study and continued into the double-blind safety extension study (D3820C00007).

A total of 11 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 ITT and safety analysis sets.

Of the 649 patients who received treatment, 17.5% discontinued the study: 18.8%, 17.1%, and 16.6% in the NKTR-118 25 mg, 12.5 mg, and placebo groups, respectively. The most

common reasons for study withdrawal were adverse events (AEs) (6.4%) and subject decision (5.5%). The proportion of patients who discontinued treatment due to AEs was higher in the NKTR-118 25 mg treatment group (10.1%) than in the 12.5 mg (4.1%) or placebo (5.1%) treatment groups.

Overall, there were no 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; 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; and treatment compliance. Most patients were taking laxatives prior to enrollment into the study. The US was the predominant region accounting for most randomized patients.

The patient population recruited to the study was considered representative of OIC patients globally with respect to demographic and disease characteristics at baseline.

Summary of efficacy results

The following table presents the primary endpoint, ie, the response (responder/non-responder) to study drug during Weeks 1 to 12.

Table S2 CMH analysis of response rate for Weeks 1 to 12 (Intent-to-treat analysis set)

Treatment Group	n	Number (%) of patients responding	Comparison versus Placebo [a]		
			RR	95% CI	p-value
Placebo	214	63 (29.4)	NA	NA	NA
NKTR-118 12.5 mg	213	87 (40.8)	1.380	(1.062, 1.795)	0.015 *
NKTR-118 25 mg	214	95 (44.4)	1.509	(1.168, 1.949)	0.001 *

* Statistically significant under the multiple testing procedure.
[a] Analysis via Cochran Mantel-Haenszel test stratified by response to laxatives at baseline (LIR, LAR, LUR).
Note: Response rate is based on the number of patients in the ITT analysis set in each treatment group.
CI confidence interval; CMH Cochran Mantel-Haenszel; ITT intent-to-treat; LAR Laxative Adequate Responder/Response; LIR Laxative Inadequate Responder/Response; LUR Laxative Unknown Responder/Response; NA Not applicable; RR Relative risk (a relative risk >1 is indicative of higher response rate on the NKTR-118 arm).
Source: Table 11.2.1.1.

Statistically significant higher response rates were observed in the NKTR-118 25 mg and 12.5 mg treatment groups compared with placebo over 12 weeks in patients with OIC (p=0.001 and 0.015, respectively). The response rate at Week 12 was 15.0 percentage points and 11.4 percentage points higher, respectively, in the NKTR-118 25 mg and 12.5 mg groups, compared with placebo.

The following results were obtained for the key secondary endpoints:

In the pre-specified LIR subgroup, statistically significant higher response rates were observed in the NKTR-118 25 mg and 12.5 mg groups (57 [48.7%] and 49 [42.6%] responding patients, respectively) compared with placebo (34 [28.8%] responding patients) over 12 weeks in patients with OIC who had inadequate response to laxatives in the past ($p=0.002$ and 0.028, respectively). The response rate at Week 12 was 19.9 percentage points and 13.8 percentage points higher, respectively, in the NKTR-118 25 mg and 12.5 mg groups, compared with placebo.

The time to first post-dose laxation was statistically significantly shorter for both the NKTR-118 25 mg and 12.5 mg treatment groups compared with placebo ($p<0.001$ for both comparisons). The NKTR-118 25 mg and 12.5 mg groups had shorter median time to first post-dose laxation compared with placebo (5.9, 20.4, and 35.8 hours, respectively).

There was a statistically significant increase in the mean number of days per week with at least 1 SBM at Week 12 in the NKTR-118 25 mg and 12.5 mg treatment groups compared with placebo: 0.82; 95% CI (0.51, 1.13); $p<0.001$ and 0.55; 95% CI (0.24, 0.86); $p<0.001$, respectively.

Regarding other secondary endpoints, for the NKTR-118 25 mg group, indication of improvement versus placebo in stool and rectal symptoms, based both on the daily diary data and PAC-SYM, were observed. Remaining secondary variables are presented in the CSR.

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 S3 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 = 213)	**NKTR-118 12.5 mg (N = 211)**	**NKTR-118 25 mg (N = 214)**
Any AE	100 (46.9)	104 (49.3)	131 (61.2)
[redacted]	[redacted]	[redacted]	[redacted]
Any SAE (including events with outcome = death)	11 (5.2)	11 (5.2)	7 (3.3)
Any AE leading to discontinuation of IP	12 (5.6)	9 (4.3)	22 (10.3)

[a] The percentages are based on the number of safety patients in each treatment group.
Note: AEs that started on or after the first dose of IP 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 includes those events that included permanent discontinuation of IP.
AE adverse event; IP investigational product; SAE serious AE.
Source: Table 11.3.2.1.1.

NKTR-118 at doses of 12.5 mg and 25 mg was generally safe and well-tolerated over 12 weeks of treatment for OIC. Most AEs were mild or moderate in intensity and the most common treatment-emergent AEs among NKTR-118 patients (abdominal pain, diarrhea, and nausea) were from the Gastrointestinal System Organ Class, and occurred more frequently in the NKTR-118 25 mg treatment group.

[redacted] There was no notable imbalance observed for the type or frequency of SAEs across treatment groups and results were dose-ordered within the NKTR-118 treatment groups for AEs that resulted in discontinuation of study treatment: the proportion of patients having an AE that resulted in discontinuation of study treatment was higher in the NKTR-118 25 mg dose group compared with the 12.5 mg dose group.

There was no notable imbalance among the treatment groups with respect to events affecting the cardiovascular system; centrally mediated opioid withdrawal signs as assessed by the Modified Himmelsbach scale, or by analysis of relevant AEs potentially related to withdrawal. There was no imbalance across the treatment groups with respect to suicidal behavior or ideation as assessed by the Columbia-Suicide Severity Rating Scale and AEs. NKTR-118 was not associated with AEs potentially related to abuse liability.

There were no clinically important changes from baseline in mean daily average or worst pain intensity in any treatment group, as measured by the NRS and 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, electrocardiogram, 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 and diastolic blood pressure, heart rate, or QTcF at any time point throughout the study, including the immediate 1 to 2 hours post first dose observation period.

[redacted]