AstraZeneca

Clinical Study Report Synopsis

Drug Substance	NKTR-118 (also known as naloxegol)
Study Code	D3820C00008
Edition Number	1

An Open-Label 52-week Study to Assess the Long-Term Safety of NKTR-118 in Opioid-Induced Constipation (OIC) in Patients with Non-Cancer-Related Pain

Study dates: First subject enrolled: 18 April 2011
Last subject last visit: 03 December 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

Of the 247 study centers selected for this study, 213 screened at least 1 patient and 184 randomized patients into the study. This study was conducted in the United States.

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 assess the long-term safety and tolerability of NKTR-118 25 mg.	Adverse events (ie, incidence, nature, and intensity of AEs, treatment-related AEs, SAEs, AEs leading to discontinuation, and AEs of special interest).	Safety
	Changes in laboratory assessments (ie, chemistry, hematology, and U/A).	
	Changes in vital signs, weight and BMI, and changes in physical examination.	
	Changes in ECGs.	
	Change from baseline in the mean NRS pain score for Weeks 1and 2, and Months 1, 2, 3, 6, 9, and 12.	
	Change from baseline in the mean daily opioid dose for randomization to Month 1, Months 1 to 3, 3 to 6, 6 to 9, and 9 to 12.	
	Observed values and change from baseline in composite score in modified Himmelsbach scale for the evaluation of centrally mediated opioid withdrawal symptoms at Week 1, and Months 1, 3, 6, 9, and 12.	
	Occurrence of suicidal behavior/suicidal ideation throughout the study based on the C-SSRS.	
Secondary	**Secondary**	
To evaluate the long-term safety and tolerability of NKTR-118 25 mg compared with Usual Care using descriptive statistics.	Note: Secondary variables are the same as those reported above for the primary objective with the following additions:	Safety
	Adverse events for new patients were analyzed by the following subgroups (age [<65 versus ≥65; and ≤50, >50 to ≤65, >65 to ≤75, and >75], gender, race [White, Black or African American, other], BMI [≤30 versus >30], LIR status, and baseline morphine equivalent units [<200 morphine equivalent dose units (MEU)/day versus ≥200 MEU/day]).	

Objectives	Outcome variables	Type
	Laboratory, vital signs and ECG results were analyzed for different age groups (<65 versus ≥65).	
	Mean bisacodyl dose per week for NKTR-118 patients from randomization to Month 1, and Months 1 to 3, 3 to 6, 6 to 9, and 9 to 12.	Study Subjects
Exploratory	**Exploratory**	
To collect and store deoxyribonucleic acid (DNA) for future exploratory research, and assess healthcare resource utilization	DNA extracted from the optional blood samples may be used to explore relationships between genetic variability and NKTR-118 safety, tolerability, response, and OIC.	Pgx[a]
	Data on OIC Healthcare Resource Utilization captured at the site for economic modeling purposes.	Health Economics

[a] Reported separate from the CSR

AE adverse event; BMI Body mass index; CSR Clinical study report; C-SSRS Columbia-Suicide Severity Rating Scale; DNA Deoxyribonucleic acid; ECG Electrocardiogram; LIR Laxative inadequate responder/response; NRS Numeric Rating Scale; OIC opioid-induced constipation; Pgx Pharmacogenetic; SAE Serious adverse event; U/A Urinalysis

Study design

This was a Phase III, 52-week, multi-center, open-label, randomized, parallel group, safety and tolerability study of NKTR-118 versus usual care in the treatment of OIC in patients with non-cancer-related pain. This was to have been a study with global participation, but all patients ended up being enrolled from the US. Eligible patients were randomized in a 2:1 ratio to receive either NKTR-118 25 mg daily (QD) or Usual Care treatment for OIC.

Target subject population and sample size

Patients entering the study could enroll directly from 12-week pivotal study D3820C00005, directly from the 3-month safety extension (Study D3820C00007) of the 12-week pivotal study D3820C00004, or could be "new patients" who had not previously participated in a NKTR-118 study. Patients who enrolled from a previous study had no break or pause in treatment.

All patients were required to have been 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 to have reported a history of <3 spontaneous bowel movements (SBMs)/week and at least 1 OIC associated symptom at screening and a confirmed diagnosis of OIC, at the time of randomization into their initial NKTR-118 study.

Confirmed OIC was defined as: Documented <3 SBMs/week on average over the 2-week OIC confirmation period (for roll-over patients this referred to the OIC confirmation period of the previous pivotal study). 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 excluded. In addition to the SBM 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 over the 2-week OIC confirmation period were not randomized.

No formal sample size calculation was performed for this long-term safety study. The sample size determination was based on the regulatory exposure requirement (ICH E1 [1994]) that at least 300 patients had to complete 6 months of treatment with NKTR-118 25 mg and the number of patients randomized could have been adjusted during the study in order to achieve approximately 100 patients with at least 12 months of exposure to NKTR-118.

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

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

Patients assigned to Usual Care followed a laxative treatment regimen for OIC determined by the investigator according to his/her best clinical judgment, excluding peripheral μ-opioid antagonists.

Duration of treatment

The study duration was 54 to 58 weeks. New patients underwent an initial screening period lasting up to 2 weeks, a 2-week OIC confirmation period (during which the diagnosis of OIC and stability of opioid regimen were confirmed), and a 52-week treatment period, followed by a 2-week follow-up period. Patients enrolling from another study (also referred to as 'roll-over patients') did so on the last day of the treatment period of the previous study, at which time they started the 52-week treatment period, followed by the follow-up visit 2 weeks after the last dose of study drug.

Statistical methods

No formal statistical analyses were planned for any of the endpoints collected in this study. Differences between open-label NKTR-118 25 mg and Usual care, with respect to the evaluation of long-term safety and tolerability were assessed using descriptive statistics: frequency and percentages for categorical data, event rates (per 100 patient years) for selected AEs, and n, mean, standard deviation (SD), minimum, median, and maximum for continuous data. The 25th and 75th percentiles are also presented for the mHS, NRS, and mean daily opioid dose.

Summaries for the assessment of long-term safety were presented separately by new and roll-over patients.

Subject population

A total of 2393 patients enrolled, of which 2309 were new patients and 84 were roll-over patients. Of the 2309 new patients who entered the initial study period, 760 patients completed the OIC confirmation period, were randomized, and entered the open-label treatment period. In addition, 84 roll-over patients were also randomized. Of the 844 randomized new patients and roll-over patients, 99.5% received treatment, 61.1% completed the study (defined as completing the 2-week follow-up visit after the 52-week treatment period), and 34.1% received treatment and subsequently discontinued the study. Overall, 393 and 317 patients, had at least 6 and 12 months exposure to NKTR-118 25 mg, respectively, in this study, which met the specified exposure requirements.

Of the 844 patients randomized, a total of 288 patients (34.1%) who received treatment discontinued the study for any reason: 36.8% in the NKTR-118 25 mg group, and 28.8% in the Usual Care group. The most common reasons for study withdrawal were patient decision (12.8%) and AE (7.2%). A greater proportion of patients withdrew due to AE in the NKTR-118 25 mg group (9.9%) compared with the Usual Care group (1.8%), primarily driven by GI AEs.

Overall, there were no imbalances between the NKTR-118 25 mg and Usual Care treatment groups in terms of patient characteristics that could have a potential influence on the results and their interpretation. The treatment groups were generally balanced with respect to: disposition; protocol deviations; demographic and baseline characteristics; pre-, post-, 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.

Patient characteristics for new and roll-over patients were generally similar. Patients in the Usual Care treatment group were treated according to the investigator's clinical judgment with most patients taking laxatives (79%) at the start of the treatment period, and 73% continuing on their initial laxative treatment during the study. All randomized patients were from the US.

Summary of efficacy results

- For the NKTR-118 25 mg treatment group, use of rescue medication was low and stable over the treatment period.

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 S1 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]	
	Usual Care (N = 270)	**NKTR-118 25 mg (N = 534)**
Any AE	195 (72.2)	437 (81.8)
Any AE with outcome = death	1 (0.4)	1 (0.2)
Any SAE (including events with outcome = death)	30 (11.1)	51 (9.6)
Any AE leading to permanent discontinuation of IP	NA	56 (10.5)

[a] The percentages are based on the number of patients in the safety analysis set in each treatment group and patient group.

Note: AEs that started on or after the first dose of study drug (NKTR-118 25 mg or Usual care) 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 25 mg was generally safe and well-tolerated in this open-label 52-week long-term safety study of OIC patients. Most AEs were mild or moderate in intensity and the most common treatment-emergent AEs in the NKTR-118 25 mg treatment group were: abdominal pain, diarrhea, nausea, headache, and flatulence and occurred more frequently in the NKTR-118 25 mg treatment group compared with the Usual Care group.

Two deaths of unknown cause were reported: 1 patient in the NKTR-118 25 mg group (preferred term: idiopathic generalized epilepsy) on Day 111 (35 days after last dose of IP), and 1 patient in the Usual Care treatment group (preferred term: death) on Day 95, neither of which was considered by the investigator to be related to study treatment. There was no notable imbalance observed for the type or frequency of SAEs between treatment groups. The most common AEs leading to discontinuation of IP in the NKTR-118 25 mg treatment group were gastrointestinal AEs. A predominance of GI AEs is not unexpected given the disease under study and the mechanism of action of NKTR-118.

There was no imbalance between 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 notable imbalance between 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 average pain intensity scores in either treatment group, as measured by the NRS and analysis of mean daily opioid dose showed no clinically important increase or decrease in either treatment group.

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.