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A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy, safety, and tolerability of naloxegol in patients with opioid-induced constipation

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ABSTRACT

Naloxegol (previously known as NKTR-118) is a peripherally acting μ-opioid receptor antagonist engineered using polymer conjugate technology in development as an oral, once-daily agent for the treatment of opioid-induced constipation (OIC). Eligible patients with OIC (n = 207), defined as <3 spontaneous bowel movements (SBMs) per week with accompanying symptoms, on a stable opioid regimen of 30–1000 mg/day morphine equivalents for ⩾2 weeks were randomized to receive 4 weeks of double-blind placebo or naloxegol (5, 25, or 50 mg) once daily in sequential cohorts after a 1-week placebo run-in. The primary end point, median change from baseline in SBMs per week after week 1 of drug administration, was statistically significant for the 25- and 50-mg naloxegol cohorts vs placebo (2.9 vs 1.0 [$P = 0.0020$] and 3.3 vs 0.5 [$P = 0.0001$], respectively). The increase in SBMs vs placebo was maintained over 4 weeks for naloxegol 25 mg (3.0 vs 0.8 [$P = 0.0022$]) and 50 mg (3.5 vs 1.0 [$P < 0.0001$]). Naloxegol was generally well tolerated across all dosages. The most frequent adverse events (AEs) were abdominal pain, diarrhea, and nausea. Most AEs at 5 and 25 mg/day were mild and transient. Similar AEs occurred with increased frequency and severity in the 50-mg cohort. There was no evidence of a statistically significant increase from baseline in pain, opioid use for the 25- and 50-mg cohorts, or centrally mediated opioid withdrawal signs and/or symptoms with naloxegol. These data demonstrate that once-daily oral naloxegol improves the frequency of SBMs compared with placebo and is generally well tolerated in this population of patients with OIC.

1. Introduction

Opioids are effective analgesics for treating moderate to severe pain, but their use is often limited by adverse effects. Gastrointestinal (GI) side effects are among the most troublesome in terms of frequency and severity [5]. Examples include abdominal cramping, bloating, nausea, vomiting, dyspepsia, and constipation [4,9,10]. Up to 60% of patients experience opioid-induced constipation (OIC), to which patients rarely develop tolerance [9,10] and which can lead them to reduce or abandon opioid therapy [5].

OIC is believed to result primarily from agonist stimulation of μ-opioid receptors in the enteric nervous system, leading to decreased gastric motility and emptying, diminished intestinal secretions, and decreased motility in the small and large intestine [5,9,10]. Common treatment involves the use of laxatives (eg, stool softeners, stimulants, osmotic agents, combination agents, and/or bulking agents) together with nonpharmacologic strategies such as increased dietary fiber, fluid intake, and exercise [9]. However, many patients do not experience adequate symptom relief, because currently available therapies do not address the underlying pathophysiology of OIC [5,6,11].

Opioid antagonists represent a possible alternative to laxatives for the treatment of OIC [5]. However, in the absence of properties

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restricting blood–brain barrier penetration, opioid antagonists can generate central effects leading to inadequate pain control and/or central opioid withdrawal signs and/or symptoms [7]. Administration of selective, peripherally acting μ-opioid receptor antagonists represents a rational and targeted approach to reducing the adverse GI effects of opioid therapy without reversing the centrally mediated analgesic effects essential for maintaining adequate pain control [5].

Naloxegol (previously known as NKTR-118) is a polymer conjugate of the opioid antagonist naloxone in clinical development as a once-daily oral treatment for OIC [1,12]. It was specifically designed as a peripheral opioid antagonist of μ-opioid receptors outside of the central nervous system, incorporating a polyethylene glycol moiety that limits its capacity to cross the blood–brain barrier [1–3]. This randomized, double-blind, placebo-controlled, phase 2, dose-escalation study evaluated the efficacy and safety of 3 dose levels of oral naloxegol with regard to the frequency of spontaneous bowel movements (SBMs) in patients with OIC.

2. Methods

2.1. Patients

Men and nonpregnant, nonbreastfeeding women who were 18 years of age or older were eligible for this study. Patients must have been receiving a stable oral opioid regimen of 30 to 1000 mg/day oral morphine equivalent doses to treat nonmalignant or cancer-related pain for at least 2 weeks before screening, with no change in dose anticipated for the duration of the study. Eligible patients were stratified as low opioid baseline group (30–100 daily morphine equivalent units [MEU]) and high opioid baseline group (>100–1000 daily MEU). Documentation of OIC, defined as $\leqslant$5 SBMs during the 2-week run-in period (which corresponds with <3 SBMs per week), was required. Patients were required to have self-reported OIC (<3 SBMs per week) and at least one of the following signs and symptoms at the initial screening visit and during the 2-week run-in period: hard/lumpy stools, straining, or sensation of incomplete evacuation/anorectal obstruction. Patients also had to be willing to stop the use of all laxatives and other bowel regimens throughout the 2-week run-in period and the 5-week treatment period.

Patients with evidence of renal or hepatic disease were excluded if they had serum creatinine >2× upper limit of normal (ULN), serum alanine transaminase or aspartate transaminase >3× ULN, serum bilirubin >2.5× ULN, or cirrhosis. Patients with ischemic heart disease or other medical conditions that would unduly increase risk to the patient or affect the interpretation of study data were excluded, as were patients with a life expectancy <6 months. A history of GI hemorrhage related to GI pathology or fecal incontinence, irritable bowel syndrome, inflammatory bowel disease, intestinal obstruction, or other active GI disorder associated with diarrhea, intermittent loose stools, or constipation prohibited study eligibility. Patients using manual maneuvers to induce a bowel movement were not eligible for study enrollment.

2.2. Study design

This was an international, multicenter, randomized, double-blind, placebo-controlled, dose-escalation phase 2 study (NCT00600119). Following an initial 10-day screening period, eligible patients underwent an additional 2-week run-in period to confirm diagnosis of OIC (Fig. 1). During this period, patients were required to discontinue use of all laxatives and other bowel regimens. Bisacodyl was the only rescue medication allowed if an SBM had not occurred in a 72-hour period since the previous bowel movement. In addition, patients entered the following data on a daily basis in an electronic diary: bowel movements, pain scores, unscheduled use of opioid medications for pain, and bisacodyl rescue use (if needed). Only patients with confirmed OIC and who continued to fulfill all the entry criteria were randomized and entered a 1-week single-blind placebo run-in period followed by a 4-week double-blind treatment period with naloxegol or placebo. The placebo run-in period was included to establish baseline pain control and allow assessment of placebo effect.

The study was planned to include 4 sequential dose cohorts of naloxegol once daily (5 mg [cohort 1], 25 mg [cohort 2], 50 mg [cohort 3], and 100 mg [cohort 4]), with 54 patients randomized in a 1:1 ratio of active:placebo within each cohort. Randomization was stratified to low (30–100 MEU/day) and high (>100–1000 MEU/day) MEU daily opioid dose based on the patient's total daily opioid dose at baseline using an Interactive Voice Response System. Dose escalations would occur only after a thorough analysis of aggregate safety data from the current cohort, including pain progression, possible opioid withdrawal signs and/or symptoms, daily opioid use, and reported adverse events.

Study medication, consisting of a 4% oral solution of naloxegol or placebo, was prepared by the unblinded study pharmacist and dispensed to the patient in a blinded manner via prefilled syringes at the time of a patient's clinic visit. The study medication was then self-administered by the patient orally via 1-mL (5- and 25-mg cohorts) or 3-mL (50-mg cohort) syringes once daily at least 1 hour before breakfast. Total volumes of each dose of study medication were 0.125 mL, 0.625 mL, and 1.25 mL for the 5-, 25-, and 50-mg cohorts, respectively. Patients and all study personnel were blinded except for the site monitor responsible for monitoring drug accountability and the site pharmacist and/or designated staff who prepared the study medication.

All study participants provided written informed consent before initiation of any study procedures. The protocol, amendments, and all study-related material were approved by an institutional review board. The study was conducted in accordance with good clinical practice and ethical principles as described in guidelines of the International Conference of Harmonisation, the United States Code of Federal Regulations, and the Declaration of Helsinki.

2.3. Assessments

The primary efficacy end point was change in SBMs/week from baseline to the end of week 1 of the double-blind treatment period. An SBM was defined as a bowel movement that occurred without the use of a rescue laxative within the previous 24 hours. Baseline SBMs per week were determined during the 2-week run-in period. The number and timing of bowel movements was recorded daily using electronic diary devices.

Secondary efficacy end points included change from baseline in SBMs per week for each of weeks 2, 3, and 4 of the double-blind treatment period; change from baseline in SBMs per week across the 4-week double-blind treatment period; and time from first dose of study drug to first laxation. Patients also completed the Patient Assessment of Constipation-Symptom Questionnaire (PAC-SYM), Patient Assessment of Constipation-Quality of Life Questionnaire (PAC-QoL), and Short Form Health Survey (SF-36) at the investigator site on day 1 of the double-blind treatment period before the first dose of study drug, on day 1 of week 2 of double-blind treatment, and at the end of double-blind treatment. The PAC-SYM includes 12 items in 3 domains: abdominal symptoms, rectal symptoms, and stool symptoms. Each item was scored on a 5-point scale from 0 = absence of symptoms to 4 = very severe. The PAC-QoL has 28 items that are included in 4 subscales: