Phase I, Randomized, Double-Blind, Placebo-Controlled Studies on the Safety, Tolerability, and Pharmacokinetics of Naldemedine in Healthy Volunteers

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Abstract

Naldemedine (S-297995) is a peripherally acting μ-opioid receptor antagonist for the treatment of opioid-induced constipation, a common side effect of opioid therapy. We determined the safety, tolerability, and pharmacokinetic profiles of oral naldemedine in healthy volunteers in 2 randomized, double-blind, placebo-controlled, phase 1 studies. In the single ascending dose study, subjects received a single dose of naldemedine (0.1-100 mg; n = 42) or placebo (n = 14). In the multiple ascending dose study, subjects received once-daily naldemedine (3-30 mg; n = 27) or placebo (n = 9) for 10 days. On day 1 of the single ascending dose studies and day 10 of the multiple ascending dose studies, respectively, the maximum plasma concentration levels of naldemedine were 1.98 to 2510 ng/mL and 73.8 to 700 ng/mL, peaked at 0.5 hours and 0.5 to 0.75 hours, and the fraction excreted in urine was 15.9% to 20.5% and 19.7% to 19.1%. There were no major safety or tolerability concerns even at naldemedine doses 150 to 500 times the therapeutic dose of 0.2 mg. The incidence of adverse events was not dose dependent. Gastrointestinal adverse events occurred more frequently with naldemedine vs placebo, and all of these were considered treatment related. Overall, naldemedine was rapidly absorbed, and no safety or tolerability issues were noted at the doses evaluated.

Keywords

naldemedine, opioid-induced constipation, peripherally acting μ-opioid receptor antagonist, pharmacokinetics, safety

Opioid-induced constipation (OIC) is a frequent and debilitating side effect of opioid analgesics, which are widely used to manage moderate to severe chronic pain. Unlike other side effects of opioids, OIC is generally not self-limiting.¹,² OIC is characterized by reduced frequency of bowel movements, development or worsening of straining, a sense of incomplete evacuation, and hard stools after the initiation of opioid therapy.³,⁴ Opioids act on the μ-, δ-, and κ-opioid receptors distributed widely in the central and peripheral nervous systems. Although the role of δ- and κ-opioid receptors in causing gastrointestinal adverse events (AEs) is less clear, the importance of μ-opioid receptors is better understood. The stimulation of μ-opioid receptors, which are expressed throughout the gastrointestinal tract, alters neural activity in the submucosal and myenteric plexuses of the enteric nervous system. These alterations can lead to impairment of gastrointestinal fluid secretion and motility, along with increased fluid absorption, resulting in OIC.⁵,⁶

Laxatives are often used as first-line treatment for OIC, but many patients do not achieve satisfactory relief of constipation.⁴,⁶ A targeted pharmacological treatment for OIC is peripherally acting μ-opioid receptor antagonists (PAMORAs). PAMORAs aim to reverse OIC by blocking the action of opioids at peripheral μ-opioid receptors in the gastrointestinal tract without affecting analgesia.⁴ Naldemedine

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(S-297995; Symproic®), a PAMORA, was approved in March 2017 for the treatment of OIC in adults with chronic noncancer pain (United States and Japan) and in cancer patients (Japan). The structure of naldemedine, an amide derivative of the opioid receptor antagonist naltrexone, limits its ability to cross the blood-brain barrier. Naldemedine has 5 metabolites: nor-naldemedine; benzamidine; naldemedine-carboxylic acid (naldemedine CA); naldemedine 3-O-β-D-glucuronide (naldemedine 3-G); and naldemedine 6-O-β-D-glucuronide (naldemedine 6-G; Figure 1). The primary metabolic pathway for naldemedine is via CYP3A to nor-naldemedine, and to a lesser extent via UDP-glucuronosyltransferase 1A3 to naldemedine 3-G and naldemedine 6-G. The drug is also cleaved in the gastrointestinal tract to form benzamidine and naldemedine CA. With respect to the activity of metabolites, the antagonist activity of the metabolites for the μ-opioid receptor is at least 20 times lower than that of the parent drug.

This article details 2 randomized, placebo-controlled, double-blind phase 1 trials: the single ascending dose (SAD) study and the multiple ascending dose (MAD) study. The results from these phase 1 studies were used to support further development of clinical trials with naldemedine. Recent publications demonstrate the safety and efficacy of naldemedine in phase 2b and phase 3 trials in patients with OIC and cancer or chronic noncancer pain. Of note, naldemedine is the first oral PAMORA with demonstrated efficacy in patients with OIC who are receiving opioids for the management of cancer pain. Here we report results from the phase 1 studies, including the first-in-human study, that evaluate the safety, tolerability, and pharmacokinetic (PK) profiles of naldemedine and its metabolites in healthy adults.

**Subjects and Methods**

**Study Design**

We conducted 2 randomized, double-blind, placebo-controlled, phase 1 trials in healthy male Japanese volunteers (SAD and MAD studies) to determine the safety, tolerability, and PK parameters of naldemedine. All subjects provided written informed consent prior to participating in the studies. Both studies were conducted at a single study center (Medical Corporation Shinanokai, Shinanozaka Clinic, Tokyo, Japan), approved by the Institutional Review Board (IRB of Shinanokai, Shinanozaka Clinic, Tokyo, Japan), and were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and the International Conference of Harmonisation Good Clinical Practice.

In both studies subjects were randomly assigned in a 3:1 ratio to receive naldemedine or placebo. On day 1 of the SAD study, subjects received a single oral dose of 0.1, 0.3, 1, 3, 10, 30, or 100 mg of naldemedine or placebo with 60 mL Japanese Pharmacopeia water for injection (sterile water used to assist with oral administration of the drug). In the MAD study, subjects received once-daily oral doses of 3, 10, or 30 mg of naldemedine or placebo with 180 mL of
Japanese Pharmacopeia water for injection for 10 days. In the SAD study (N = 56), each dose group consisted of 8 subjects (naldemedine, n = 6; placebo, n = 2). In the MAD study (N = 36), there were 12 subjects per dose group (naldemedine, n = 9; placebo, n = 3).

In the SAD study, subjects fasted from 10 PM on the evening before dosing to 4 hours postdosing. On each treatment day of the MAD study, subjects fasted from 10 hours before dosing to 3 hours postdosing. In step 1 of the SAD study, the safety and tolerability of the 0.1-mg dose of naldemedine were first confirmed in a subset of subjects (n = 4), after which, administration continued in the remaining subjects (n = 4). In both studies, dosing started at the lowest dose and proceeded stepwise to the next higher dose. Before each dosing step, test results collected from each subject were fully examined to determine the validity of proceeding to the next step.

Eligibility Criteria
Healthy male Japanese volunteers aged ≥20 years to <40 years, with body weights of ≥50 kg to ≤80 kg and body mass indices of ≥18.5 kg/m² to <25.0 kg/m² were eligible to participate. Eligible subjects were not using any drugs containing opioids during the 2 weeks before screening and admission to the study.

Pharmacokinetic Profile Assessments
Blood and urine samples were collected and analyzed at several time points to determine the concentration of naldemedine and its metabolites. On day 1 of the studies, blood samples were collected predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours postdose. Additional blood samples were collected at 3.5, 4.5, 24, and 32 hours postdose in the SAD study, and at 0.75 hours postdose in the MAD study. On days 2 to 10 of the MAD study, blood samples were collected immediately after administration of the drug. On day 10 of the MAD study, blood samples were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose. On day 1 of each study, urine samples were collected before administration of the drug. In the SAD study, urine samples were collected at postdosing periods of 0 to 6 hours, 6 to 12 hours, and 12 to 24 hours. On days 1 and 10 of the MAD study, urine samples were collected at postdosing periods of 0 to 12 hours and 12 to 24 hours.

The plasma and urinary concentration levels of naldemedine and its metabolites were determined by liquid chromatography coupled with tandem mass spectrometry methods using a Shimadzu. LC 10A or 20A high-performance liquid chromatography (Shimadzu Corporation, Kyoto, Japan) and SCIEX API 5000 mass spectrometer (AB SCIEX, Framingham, Massachusetts) systems. Stable isotope-labeled internal standard solution and 100 mmol/L ammonium formate (pH 9.5) were added to plasma samples (100 μL) and applied to a solid-phase extraction cartridge (Sep-Pak tC18, 100 mg, Waters Corporation, Tokyo, Japan). Naldemedine and its metabolites were extracted using methanol/formic acid (50:1), evaporated under nitrogen stream, and dissolved with 100 mmol/L ammonium formate/75% methanol (1:1). For the preparation of urine samples, internal standard solution and methanol were added to 200 μL of urine/2-propanol (1:1), and the supernatant was diluted with 100 mmol/L ammonium formate. Aliquots of plasma (15 μL) and urine (20 μL) extracts were injected into the high-performance liquid chromatography system and separated by a mixed-mode column of strong cation-exchange (CAPCELL PAK CR 1:20 column, 2 mm × 150 mm; 5 μm) and reversed phase using a gradient elution of mobile phase A (water/1 mol/L ammonium formate/formic acid [990:10:1]) and mobile phase B (acetonitrile/methanol/2-propanol/water/1 mol/L ammonium formate/formic acid [400:400:100:90:10:1]) at a flow rate of 0.6 mL/min.

Mass spectrometry was performed in the positive electrospray ionization mode using multiple reaction monitoring with m/z transitions of 571 → 368 for naldemedine, 747 → 368 for naldemedine 6-G, 747 → 544 for naldemedine 3-G, 517 → 314 for nor-naldemedine, 471 → 368 for naldemedine CA, 121 → 104 for benzamidine, 577 → 368 for naldemedine-15Nd5, 753 → 368 for naldemedine 6-G-15Nd5, 753 → 544 for naldemedine 3-G-15Nd5, 522 → 314 for nor-naldemedine-d5, 477 → 368 for naldemedine CA-d6, and 135 → 118 for 4-methylbenzamidine.

Plasma and urine samples were analyzed using validated methods. Calibration curves were linear over plasma analyte concentration ranges of 0.01 to 10 ng/mL for naldemedine; 0.04 to 40 ng/mL for naldemedine 3-G, naldemedine 6-G, nor-naldemedine, and naldemedine CA; and 0.3 to 30 ng/mL for benzamidine. Within-run precision, between-run precision, and accuracy of all of the analytes were 1.7%, 11.1%, 3.3% to 10.8%, and –5.3% to 6.0%, respectively. Calibration curves were linear over urine analyte concentration ranges of 0.1 to 100 ng/mL for naldemedine; 0.4 to 400 ng/mL for naldemedine 3-G, naldemedine 6-G, nor-naldemedine, and naldemedine CA; and 0.2 to 200 ng/mL for naldemedine 6-G, and 3 to 100 ng/mL for benzamidine. Within-run precision, between-run precision, and accuracy for the analytical method in urine were 2.6% to 9.0%, 5.3% to 9.6%, and –3.3% to 9.4%, respectively.

In both studies plasma and urinary concentration levels of naldemedine and its metabolites were used to calculate the maximum observed plasma concentration (Cmax), time to Cmax, apparent terminal elimination half-life, apparent total plasma clearance, and the
fraction excreted in urine (Feu; elimination half-life and Feu were calculated for unchanged naldemedine only). Feu was calculated from

$$\text{Feu} = \frac{\text{Ae}_{\text{0-24h}}}{\text{Dose}} \times 100$$

where \(\text{Ae}_{\text{0-24h}}\) is the amount of urinary excretion calculated from urinary concentration levels and urine volume.

In the SAD study the area under the plasma concentration-time curve (AUC) from time 0 to the time of the last measurable concentration (AUC_{0-last}) was calculated. On day 1 of the SAD and MAD studies, the AUC from time 0 extrapolated to infinity (AUC_{inf}) was calculated. The AUC from 0 to the time point of the dosage interval (AUC_{0-t}) was calculated for the MAD study only. AUC_{0-last}, AUC_{inf}, and AUC_{0-t} were calculated using the linear trapezoidal method. In the SAD study \(C_{\text{max}}\) and AUC of naldemedine were examined for dose dependency. In the MAD study \(C_{\text{max}}\) and AUC, after the initial dose of naldemedine on day 1 and following multiple dosing on day 10, were compared to evaluate accumulation and time dependency.

**Safety Assessments**

In both studies the safety and tolerability of naldemedine were assessed in all subjects by monitoring symptoms, vital signs, safety electrocardiogram recordings, and clinical laboratory evaluations (hematology, blood chemistry tests, and urinalysis). Throughout the duration of the studies, subjects were also monitored for AEs with respect to severity, outcome, and relationship to the study drug.

**Statistical Analysis**

In the SAD study approximately 77 subjects were planned for enrollment, encompassing 56 subjects (8 for each dose level) who were expected to meet the eligibility criteria, plus 21 subjects in reserve. In the MAD study 45 subjects were planned for enrollment, encompassing 56 subjects (8 for each dose level) who were expected to meet the eligibility criteria, plus 21 subjects in reserve. In the SAD study (minimum/maximum naldemedine plasma trough concentrations at 3-mg dose were 3.12/3.66 ng/mL; at 10-mg dose 7.48/9.23 ng/mL; and at 100-mg dose 18.3/20.9 ng/mL). In the SAD study the metabolic ratio (MR_{AUC}) for the AUC_{0-inf} of nor-naldemedine (the main metabolite of naldemedine) to the AUC_{0-inf} for naldemedine was 20.1% to 28.6% within the dose range of 0.1 mg to 100 mg. The geometric mean of the MR_{AUC} for AUC_{0-inf} of naldemedine 3-G and naldemedine 6-G was <3% and <1%, respectively. The plasma concentrations of benzamidine were mostly below the lower limit of quantification (0.3 ng/mL) in the dose range of 0.1 mg to 10 mg. The AUC_{0-inf} and MR_{AUC} for benzamidine could not be calculated because of insufficient elimination-phase data. The geometric mean of the MR_{AUC} for AUC_{0-last} of benzamidine was <1% in the 30- and 100-mg dose groups. On day 10 of the MAD study, the MR_{AUC} for nor-naldemedine, benzamidine, and naldemedine 3-G were approximately 20%, 7%, and 2%, respectively, across all tested doses. An exception was observed for benzamidine after multiple daily doses of 3 mg, in which almost all concentrations were below the lower limit of quantification. The MR_{AUC} for naldemedine 6-G and naldemedine CA were <1%.

**Results**

**Subject Disposition**

Of the 56 subjects randomized in the SAD study, 42 subjects received naldemedine (6 subjects per dose), and 14 subjects received placebo (2 subjects per dose). Of the 36 subjects randomized in the MAD study, 27 subjects received naldemedine (9 subjects per dose), and 9 subjects received placebo (3 subjects per dose). All randomized subjects completed the studies. The safety analysis population included all randomized subjects in the SAD (n = 56) or MAD (n = 36) studies. The PK analysis population consisted of all subjects who received naldemedine in the SAD (n = 42) or MAD (n = 27) studies. The baseline characteristics of subjects were comparable across treatment groups in both studies (Table 1).

**Pharmacokinetic Parameters**

Results from the SAD study indicate AUC_{inf} and C_{max} of naldemedine were dose dependent and almost dose proportional (Table 2 and Figure 2). Naldemedine was rapidly absorbed in the SAD and MAD studies (Figure 3). In the MAD study C_{max} of naldemedine increased by 1-fold to 1.3-fold, and AUC_{0-t} increased by 1-fold to 1.2-fold. Time to C_{max} remained relatively constant at 0.5 to 0.75 hours for all tested doses in both studies (Table 2). The plasma trough concentration levels of naldemedine were relatively stable from days 2 to 10 in the MAD study (minimum/maximum naldemedine plasma trough concentrations at 3-mg dose were 3.12/3.66 ng/mL; at 10-mg dose 7.48/9.23 ng/mL; and at 100-mg dose 18.3/20.9 ng/mL). In the SAD study the metabolic ratio (MR_{AUC}) for the AUC_{0-inf} of nor-naldemedine (the main metabolite of naldemedine) to the AUC_{0-inf} for naldemedine was 20.1% to 28.6% within the dose range of 0.1 mg to 100 mg. The geometric mean of the MR_{AUC} for AUC_{0-inf} of naldemedine 3-G and naldemedine 6-G was <3% and <1%, respectively. The plasma concentrations of benzamidine were mostly below the lower limit of quantification (0.3 ng/mL) in the dose range of 0.1 mg to 10 mg. The AUC_{0-inf} and MR_{AUC} for benzamidine could not be calculated because of insufficient elimination-phase data. The geometric mean of the MR_{AUC} for AUC_{0-last} of benzamidine was <1% in the 30- and 100-mg dose groups. On day 10 of the MAD study, the MR_{AUC} for nor-naldemedine, benzamidine, and naldemedine 3-G were approximately 20%, 7%, and 2%, respectively, across all tested doses. An exception was observed for benzamidine after multiple daily doses of 3 mg, in which almost all concentrations were below the lower limit of quantification. The MR_{AUC} for naldemedine 6-G and naldemedine CA were <1%.
Table 1. Subject Baseline Characteristics in the SAD (A) and MAD (B) Studies

(A) SAD Study

| Parameter, Mean (SD) | 0.1 mg (n = 6) | 0.3 mg (n = 6) | 1 mg (n = 6) | 3 mg (n = 6) | 10 mg (n = 6) | 30 mg (n = 6) | 100 mg (n = 6) | Pooled Placebo (n = 14) |
|----------------------|----------------|----------------|-------------|-------------|-------------|-------------|--------------|-------------------------|
| Age, y               | 26.5 (5.3)     | 24.8 (2.1)     | 24.5 (1.6)  | 27.8 (8.1)  | 24.7 (3.5)  | 24.7 (2.6)  | 21.8 (1.6)   | 23.8 (3.8)               |
| Height, cm           | 170.80 (4.37)  | 172.60 (4.00)  | 170.40 (4.41)| 169.80 (5.87)| 175.05 (4.17)| 166.07 (4.55)| 167.95 (6.21)| 171.84 (5.15)            |
| Weight, kg           | 64.22 (6.35)   | 64.48 (7.26)   | 65.47 (4.49) | 61.92 (8.24) | 66.23 (4.10) | 56.77 (4.45) | 57.50 (4.83) | 61.20 (6.32)             |
| BMI, kg/m²           | 21.95 (1.28)   | 21.62 (1.85)   | 22.60 (2.15) | 21.35 (1.44) | 21.67 (1.85) | 20.58 (1.49) | 20.37 (0.96) | 20.70 (1.61)             |

(B) MAD Study

| Parameter, mean (SD) | 3 mg (n = 9) | 10 mg (n = 9) | 30 mg (n = 9) | Pooled Placebo (n = 9) |
|----------------------|-------------|--------------|--------------|------------------------|
| Age, y               | 28.4 (7.1)  | 27.6 (4.8)   | 28.3 (5.0)   | 27.8 (5.3)              |
| Height, cm           | 173.57 (4.88)| 173.91 (4.54)| 172.93 (5.90)| 174.09 (5.93)           |
| Weight, kg           | 63.40 (6.61)| 63.67 (5.18) | 62.70 (6.94) | 65.12 (7.12)            |
| BMI, kg/m²           | 21.03 (1.95)| 21.04 (1.27) | 20.93 (1.80) | 21.48 (2.17)            |

BMI indicates body mass index; MAD, multiple ascending dose; SAD, single ascending dose; SD, standard deviation.

aPharmacokinetic analysis population (included subjects in the naldemedine dosing groups).

bSafety analysis population (included subjects in the naldemedine and placebo groups).

The mean plasma concentration-time curves of unchanged naldemedine and its metabolites were generally similar in trend between the SAD and MAD studies (Figure 4). In the SAD study the geometric means of Feu of unchanged naldemedine over 24 hours were 15.9% to 23.1% within the range of 0.1 mg to 100 mg, and for benzamidine were 7.4% to 12.7% within the range of 0.3 mg to 100 mg. In the MAD study the geometric means of Feu over 24 hours after administration of 3 to 30 mg of naldemedine on days 1 and 10 were 15.3% to 19.7%, respectively. The major naldemedine metabolite in urine was benzamidine, and the geometric mean of Feu on day 1 and day 10 ranged from 7.8% to 8.7% and 22.1% to 27.6%, respectively. In both studies the Feu values for nor-naldemedine, naldemedine 3-G, naldemedine 6-G, and naldemedine CA were <1%.

Safety and Tolerability

The incidence of AEs did not increase with escalating doses (Table 3). Naldemedine was not associated with any major safety or tolerability concerns at single doses up to 100 mg (Table 3A) or multiple doses up to 30 mg once daily for 10 days (Table 3B). All of the gastrointestinal AEs reported in both studies were considered to be treatment related. No deaths, AEs leading to withdrawal, or serious AEs were reported in either study. Furthermore, there were no clinically significant abnormalities in vital signs or electrocardiogram data at any of the tested naldemedine doses (data not shown).

Discussion

Systemic exposure to naldemedine was almost dose proportional within the dose range of 0.1 mg to 100 mg. In the MAD study, AUC_{inf} on day 1 and AUC_{0-τ} on day 10 were similar, suggesting that the PKs of naldemedine are time independent. Absorption of naldemedine in the fasted state was rapid (0.5 to 0.75 hours), and slight accumulations in the C_{max} (1-fold to 1.3-fold) and AUC (1-fold to 1.2-fold) of naldemedine were observed. The relatively constant plasma trough concentration levels of naldemedine from days 2 to 10 for all tested doses in the MAD study suggest that the PK of naldemedine reached a steady state within 2 days of treatment.

In the United States, only 2 other PAMORAs are approved for the treatment of OIC: methylnaltrexone bromide and naloxegol. Naldemedine is the only oral PAMORA with demonstrated efficacy and favorable safety profile in patients with OIC and cancer. Another potential benefit of naldemedine is its posology. A comparably lower dose of naldemedine (0.2 mg × 1 tablet) is required to achieve a similar efficacy and safety profile to that observed with methylnaltrexone bromide (150 mg × 3 tablets) or naloxegol (12.5 to 25 mg × 1 tablet). The PK profile of naldemedine appears to be distinct from those of the other compounds at doses close to their respective therapeutic doses. Specifically, a single oral dose of naldemedine at 0.3 mg was associated with a much lower C_{max} vs methylnaltrexone bromide at 19.2 mg/kg or naloxegol at 30 mg...
Table 2. Pharmacokinetic Parameters of Naldemedine in the SAD Study (A) and Day 1 and Day 10 of the MAD Study (B)

**(A) SAD Study**

| Naldemedine     | C_{max} (ng/mL) | T_{max}^a (h) | AUC_{0-last} (ng·h/mL) | AUC_{inf} (ng·h/mL) | t_{1/2,z} (h) | CL/F (L/h) | Feu (%)  |
|-----------------|-----------------|---------------|------------------------|---------------------|--------------|------------|----------|
| 0.1 mg (n = 6)  | G mean (CV,%)   | 1.98 (30.9)   | 0.50 (0.50, 1.0)       | 10.99 (24.6)        | 8.30 (9.8)   | 8.62 (25.4) | 15.9 (29.2) |
|                 | A mean (SD)     | 2.05 (0.54)   | 1.12 (2.52)            | 11.60 (25.4)        | 8.83 (0.81)  | 8.86 (24.2) | 16.4 (3.90) |
| Naldemedine 0.3 mg (n = 6) | G mean (CV,%) | 4.47 (19.3)   | 0.50 (0.25, 0.50)      | 29.68 (13.0)        | 32.53 (16.5) | 9.24 (20.4) | 9.22 (16.5) |
|                 | A mean (SD)     | 4.54 (0.83)   | 2.98 (3.81)            | 32.90 (5.31)        | 9.41 (20.5)  | 9.33 (1.54) | 17.9 (1.90) |
| Naldemedine 1 mg (n = 6) | G mean (CV,%) | 16.2 (23.0)   | 0.50 (0.50, 1.0)       | 102.9 (8.0)         | 107.7 (7.9)  | 7.56 (10.9) | 9.28 (7.9)  |
|                 | A mean (SD)     | 16.5 (3.88)   | 2.05 (0.54)            | 11.24 (2.52)        | 11.89 (2.75) | 8.33 (0.81) | 8.86 (24.2) |
| Naldemedine 3 mg (n = 6) | G mean (CV,%) | 52.2 (14.3)   | 0.50 (0.25, 0.50)      | 303.2 (16.0)        | 320.8 (15.3) | 8.13 (14.6) | 9.35 (15.3) |
|                 | A mean (SD)     | 52.6 (6.76)   | 2.98 (3.81)            | 323.8 (47.40)       | 9.41 (2.05)  | 9.33 (1.54) | 23.2 (1.97) |
| Naldemedine 10 mg (n = 6) | G mean (CV,%) | 16.2 (23.0)   | 0.50 (0.50, 1.0)       | 102.9 (8.0)         | 107.7 (7.9)  | 7.56 (10.9) | 9.28 (7.9)  |
|                 | A mean (SD)     | 16.5 (3.88)   | 2.05 (0.54)            | 11.24 (2.52)        | 11.89 (2.75) | 8.33 (0.81) | 8.86 (24.2) |

**(B) MAD Study**

| Naldemedine     | C_{max} (ng/mL) | T_{max}^a (h) | AUC_{0-last} (ng·h/mL) | AUC_{inf} (ng·h/mL) | t_{1/2,z} (h) | CL/F (L/h) | Feu (%)  |
|-----------------|-----------------|---------------|------------------------|---------------------|--------------|------------|----------|
| 3 mg (n = 9)    | G mean (CV,%)   | 56.8 (29.3)   | 0.75 (0.25, 1.5)       | 343.7 (13.5)        | 376.7 (12.8) | –          | 17.6 (19.9) |
|                 | A mean (SD)     | 58.9 (17.3)   | 346.3 (43.90)          | 379.3 (46.29)       | –            | 17.9 (3.11) |          |
| 10 mg (n = 9)   | G mean (CV,%)   | 177 (24.6)    | 0.75 (0.50, 4.0)       | 1094 (21.5)         | 1162 (23.5)  | –          | 15.3 (12.6) |
|                 | A mean (SD)     | 182 (45.2)    | 1116 (234.0)           | 1190 (273.7)        | –            | 15.4 (1.85) |          |
| 30 mg (n = 9)   | G mean (CV,%)   | 727 (26.7)    | 0.75 (0.50, 2.0)       | 3764 (13.7)         | 3921 (13.5)  | –          | 19.6 (17.0) |
|                 | A mean (SD)     | 750 (207)     | 3795 (504.7)           | 3952 (518.9)        | –            | 19.9 (3.33) |          |

Data are shown as geometric mean (G mean) and arithmetic mean (A mean) unless otherwise specified (pharmacokinetic analysis population).

A, arithmetic; AUC_{0-last}, area under the plasma concentration-time curve from time 0 to the time of the last measurable plasma concentration; AUC_{0-\tau}, area under the plasma concentration-time curve from time 0 to the time point of the dosage interval (24 hours); AUC_{inf}, area under the plasma concentration-time curve extrapolated to infinity; CL/F, apparent total plasma clearance; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; Feu, fraction excreted in urine; G, geometric; MAD, multiple ascending dose; SAD, single ascending dose; SD, standard deviation; t_{1/2,z}, apparent plasma terminal elimination half-life; T_{max}, time to maximum observed plasma concentration.

\(^a^\)Median (minimum, maximum).
AUC\textsubscript{inf} (ng*hr/mL)

Dose (mg)

Individual values
Mean (SD) values

Figure 2. Correlation between naldemedine dose and AUC\textsubscript{inf} in the SAD study (n = 6 per dosing group; pharmacokinetic analysis population). AUC\textsubscript{inf} indicates area under the plasma concentration-time curve extrapolated to infinity.

Figure 3. Mean plasma concentration-time curve of naldemedine in the SAD (A) and MAD (B) studies (day 1 and 10, 0–24 hours; pharmacokinetic analysis population). MAD indicates multiple ascending dose, single ascending dose; SD, standard deviation.

(5 ng/mL vs 166 ng/mL or 73 ng/mL, respectively). Furthermore, the AUC\textsubscript{0–inf} was lower with naldemedine vs methylaltrexone bromide or naloxegol (33 ng·h/mL vs 419 ng·h/mL or 537 ng·h/mL, respectively).\textsuperscript{15,16}

There were no safety or tolerability issues related to the administration of naldemedine as a single oral dose (0.1 to 100 mg) or as multiple oral doses (3 to 30 mg once daily for 10 days) in healthy subjects. All randomized subjects completed the study. Importantly, the doses assessed in the current studies are up to 150 to 500 times higher than the therapeutic dose of naldemedine (0.2 mg). The overall AE profiles were similar between naldemedine and placebo, although there was a numerically higher incidence of gastrointestinal disorders reported in the naldemedine group. The frequency of gastrointestinal AEs in the naldemedine group, however, was not dose dependent in the 1000-fold dose range studied. The numerically higher incidence of gastrointestinal AEs in healthy volunteers treated with naldemedine is consistent with its mechanism of action: blocking the action of opioids (including endogenous opioids).
Figure 4. Mean plasma concentration-time curves of unchanged naldemedine and its metabolites at the 3-mg dose of naldemedine on day 10 (A; 0- to 24-hour results) and on days 10 to 17 (B; semilogarithmic scale) of the MAD study (pharmacokinetic analysis population). MAD indicates multiple ascending dose; naldemedine 3-G, naldemedine 3-O-β-D-glucuronide; naldemedine 6-G, naldemedine 6-O-β-D-glucuronide; naldemedine CA, naldemedine carboxylic acid.

Furthermore, results from the phase 3, double-blind, placebo-controlled study found no imbalance in major adverse cardiovascular events in subjects treated with naldemedine 0.2 mg or placebo for 52 weeks. Together, these results suggest that naldemedine may not be associated with an increased risk for cardiovascular events. In conclusion, the results from these phase 1 studies in healthy volunteers support further investigations on the efficacy, safety, and tolerability of naldemedine for the treatment of OIC in phase 2 and phase 3 clinical trials.
Table 3. Adverse Events Reported in the (A) SAD and (B) MAD Studies (Safety Analysis Population)

(A) SAD Study

| Naldemedine Dosing Group | 0.1 mg (n = 6) | 0.3 mg (n = 6) | 1 mg (n = 6) | 3 mg (n = 6) | 10 mg (n = 6) | 30 mg (n = 6) | 100 mg (n = 6) | Pooled Naldemedine (n = 42) | Pooled Placebo (n = 14) |
|--------------------------|----------------|----------------|-------------|-------------|-------------|--------------|----------------|--------------------------|-----------------------|
| Subjects with any AE     | 2 (33.3)       | 0              | 0           | 2 (33.3)    | 1 (16.7)    | 2 (33.3)     | 9 (21.4)       | 2 (14.3)                 |                       |
| Gastrointestinal disorders |               |                |             |             |             |              |                |                          |                       |
| Abdominal discomfort     | 2 (33.3)       | 0              | 0           | 0           | 0           | 0            | 1 (2.4)        | 0                        |                       |
| Abdominal pain           | 1 (16.7)       | 0              | 0           | 0           | 1 (16.7)    | 0            | 1 (16.7)       | 2 (4.8)                 | 0                     |
| Diarrhea                 | 1 (16.7)       | 0              | 0           | 0           | 1 (16.7)    | 1 (16.7)     | 1 (16.7)       | 4 (9.5)                 | 0                     |
| Infections and infestations |              | 0              | 0           | 0           | 0           | 0            | 1 (2.4)        | 0                        |                       |
| Investigations           | 0              | 0              | 0           | 1 (16.7)    | 0           | 0            | 0              | 1 (2.4)                 | 1 (7.1)               |
| Psychiatric disorders    | 0              | 0              | 0           | 0           | 0           | 0            | 0              | 0                        | 1 (7.1)               |
| Vascular disorders       | 0              | 0              | 0           | 0           | 0           | 0            | 0              | 0                        | 1 (7.1)               |
| Subjects with treatment-related AEs | 2 (33.3) | 0              | 0           | 2 (33.3)    | 1 (16.7)    | 2 (33.3)     | 7 (16.7)       | 1 (7.1)                 |                       |

(B) MAD Study

| Naldemedine Dosing Group | 3 mg (n = 9) | 10 mg (n = 9) | 30 mg (n = 9) | Pooled Naldemedine (n = 27) | Pooled Placebo (n = 9) |
|--------------------------|-------------|--------------|---------------|---------------------------|-----------------------|
| Subjects with any AE     | 3 (33.3)    | 3 (33.3)     | 3 (33.3)      | 9 (33.3)                  | 3 (33.3)             |
| Gastrointestinal disorders |             |              |               |                           |                       |
| Abdominal discomfort     | 2 (22.2)    | 1 (11.1)     | 1 (11.1)      | 4 (14.8)                  | 1 (11.1)             |
| Diarrhea                 | 2 (22.2)    | 1 (11.1)     | 1 (11.1)      | 4 (14.8)                  | 0                     |
| Investigations           | 1 (11.1)    | 2 (22.2)     | 2 (22.2)      | 5 (18.5)                  | 2 (22.2)             |
| Subjects with treatment-related AEs | 2 (22.2) | 1 (11.1)     | 2 (22.2)      | 5 (18.5)                  | 1 (11.1)             |

AEs are shown by system organ class; gastrointestinal disorders are also presented by preferred terms.
AE indicates adverse event; MAD, multiple ascending dose; SAD, single ascending dose.

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Declaration of Conflict of Interests

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