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APPLICATION NUMBER:

208854Orig1s000

MEDICAL REVIEW(S)

Clinical Review
 Lauren Weintraub, Clinical Reviewer
 NDA 208854
 Symproic (Naldemedine Tosylate)

CLINICAL REVIEW

Application Type	NDA (Original)
Application Number(s)	208854
Priority or Standard	Standard
Submit Date(s)	March 23, 2016
Received Date(s)	March 23, 2016
PDUFA Goal Date	March 23, 2017
Division/Office	Division of Gastroenterology and Inborn Errors Products
Reviewer Name(s)	Lauren Weintraub
Review Completion Date	March 23, 2017
Established Name	Naldemedine tosylate
(Proposed) Trade Name	Symproic
Applicant	Shionogi Inc.
Formulation(s)	Oral tablet 0.2 mg
Dosing Regimen	0.2 mg orally once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

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OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

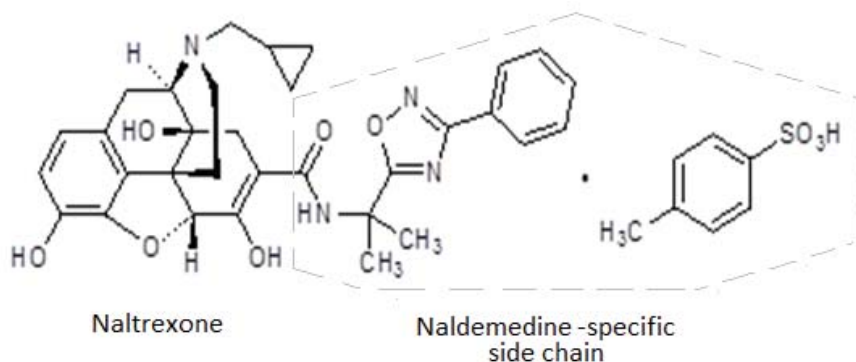
Naldemedine (proposed trade name Symproic) is a new molecular entity (NME) in the drug class of peripherally-acting opioid receptor antagonists. The proposed indication of naldemedine is the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

The to-be-marketed formulation of naldemedine is a 0.2 mg unscored, film-coated, immediate-release tablet. The proposed dosing regimen of naldemedine is 0.2 mg once daily, administered orally without regard to food intake.

Naldemedine is a derivative of the opioid antagonist, naltrexone. Naldemedine acts as an antagonist at the μ -, δ -, and κ -opioid receptors. The mechanism of action of naldemedine is the inhibition of μ -opioid receptors in the enteric nervous system of the gastrointestinal tract.

The molecular structure of naldemedine consists of the naltrexone molecule with an added side chain that increases its molecular weight and polar surface area with respect to the parent molecule. In addition, the naldemedine molecule is a substrate of the P-glycoprotein (P-gp) efflux transporter (see Figure 1). These properties decrease the ability of naldemedine to cross the blood-brain barrier. As a result, naldemedine should not antagonize the μ -opioid receptors in the central nervous system responsible for opioid-mediated analgesia.

Figure 1: Molecular Structure of Naldemedine



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1.2. Conclusions on the Substantial Evidence of Effectiveness

The effectiveness of naldemedine for treatment of OIC in adults with chronic, non-cancer pain was supported by substantial evidence from adequate and well-controlled trials in the proposed patient population interpretability of efficacy assessments. Efficacy data to support this indication were primarily obtained in 2 replicate randomized, double-blind, placebo-controlled, parallel group clinical trials that were adequately powered for the pre-specified primary efficacy analysis. The primary endpoint was the difference in proportion of responders, using a clinically meaningful, pre-specified responder definition.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Opioid analgesics are among the most commonly prescribed classes of medications, and opioid induced constipation (OIC) is the most frequently reported side effect with chronic use.[1] Unlike many other opioid-induced side effects, patients rarely develop a tolerance to the GI side effects of opioid therapy .[2] Therefore, with increasing opioid doses, OIC tends to steadily worsen despite laxative use, often leading to reduced quality of life. The GI effects of opioids are often dose-limiting, thus compromising pain control.[3] Naldemedine is an NME in the class of peripherally-acting mu-opioid receptor antagonists (PAMORA). Naldemedine and the other PAMORAs are derivatives of non-specific/global opioid antagonists to which their molecular structure has been modified to restrict passage across the blood brain barrier. As a result, these drugs act on the peripheral nervous system to address the underlying mechanisms of OIC by antagonizing the mu-opioid receptors in the gastrointestinal tract, without having the CNS pharmacologic activity of global opioid antagonists.

The effectiveness of naldemedine to treat OIC in patients with chronic non-cancer pain is supported by data from adequate and well-controlled trials in adults on stable opioid regimens for ≥4 weeks. In 2 replicate, placebo-controlled trials, superiority of naldemedine (compared to placebo) was demonstrated by primary efficacy analyses, in which statistically significant differences in the proportion of treatment responders favoring the naldemedine group were achieved, using a pre-specified, clinically-meaningful responder definition.

Gastrointestinal toxicity was the predominant type of adverse reaction observed in clinical trials, leading to treatment discontinuation in 3.2% of naldemedine-treated subjects in the pooled phase 3 safety population. Opioid withdrawal was observed in naldemedine clinical trials, occurring in ~1% of subjects and was always accompanied by GI symptoms. Although GI toxicity and, to a lesser extent, opioid withdrawal decrease tolerability of naldemedine, events were often self-limited and resolved quickly following withdrawal of treatment. Overall, serious and/or life-threatening adverse reactions were rare, and no new safety concerns were identified for this drug. This reviewer considers the degree of risk associated with this drug to be acceptable for treatment of a non-life-threatening condition. Clinical trial data were sufficient for a favorable benefit-risk assessment to support approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	Opioid analgesics are commonly prescribed for the management of moderate to severe pain and represent one of the most prescribed classes of medications worldwide. Reports estimate that more than 3% of American adults are undergoing opioid therapy for more than 3 months for chronic noncancer pain.[1] OIC is the most frequent opioid side effect, reported to affect approximately 40% of patients receiving opioids for non-malignant pain.[4] Opioids exert multiple constipating effects on the gastrointestinal (GI) tract, including slowed motility and intestinal transit, reduced inhibition of water and electrolyte secretion into the gut lumen, increased fluid absorption from the intestine, and increased anal sphincter tone.[5] Unlike other opioid effects including analgesia, patients typically do not experience tolerance to the GI effects of opioids.[2] Therefore, progressive worsening of OIC tends to occur with continued opioid use, despite use of laxatives.[3] Symptoms of OIC often impacting quality of life and can lead serious complications, such as anorexia, fecal impaction, fecal incontinence, pseudo-obstruction, impaired drug absorption, and urine retention. [5]. Due to the lack of GI tolerance to opioids, OIC can be dose-limiting and lead to inadequate pain management.[3]	Chronic opioid use for non-cancer pain is an increasing problem in the US and worldwide. Because OIC is the most common adverse reaction and does not improve with ongoing use (i.e., development of tolerance), the burden of OIC is also increasing. Although OIC is rarely life-threatening, this condition is associated with reduced quality of life and increased patient morbidity.
<u>Current Treatment Options</u>	Currently, 3 drugs are approved for the treatment of OIC in patients with chronic non-cancer pain: two peripherally-acting mu-opioid receptor antagonists (PAMORAs)—Relistor (methylnaltrexone bromide, available in both subcutaneous and oral formulations) and Movantik (naloxegol, available as an oral tablet)—and lubiprostone (Amitiza), a chloride channel activator that is also approved for the treatment of chronic idiopathic	Naldemedine is a member of the PAMORA drug class. There are currently 3 approved drugs in this class (Relistor, Movantik, and Entereg), 2 of which—Relistor and Movantik—are approved for treatment of OIC in patients with chronic non-cancer pain. These drugs target the underlying mechanism of OIC via

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	constipation (CIC) and irritable bowel syndrome (IBS). In addition to these drugs approved for OIC, standard-of-care management of OIC includes laxatives, fiber supplementation, and lifestyle interventions, such as increased fluid intake and physical activity. Though not specifically indicated for OIC, laxatives of all classes (i.e., stool softeners, bulk-forming agents, stimulants, osmotic agents, saline solutions, and lubricants) are extensively used to treat OIC and mitigate the various effects of opioids on the gastrointestinal tract (see “Analysis of Condition”). However, with long-term administration of opioids and worsening OIC, effectiveness of laxatives may lessen over time.	antagonism of opioid receptors in the gastrointestinal tract.
<u>Benefit</u>	Naldemedine is a derivative of the opioid antagonist naltrexone that binds with high affinity to mu-opioid receptors and inhibits receptor function. The molecular structure of naldemedine consists of the naltrexone molecule with an additional side chain that increases the molecular weight and the polar surface area with respect to the parent compound and reducing its ability to cross the blood-brain barrier (BBB). In addition, naldemedine is a substrate of the P-glycoprotein (P-gp) efflux transporter, another mechanism that restricts penetration of naldemedine into the CNS. By limiting drug distribution to peripheral tissues, these molecular properties enable naldemedine to reduce OIC, while limiting its interference with the CNS-mediated analgesic effects of opioids and decreasing the risk of opioid withdrawal. Evaluation of the effectiveness of naldemedine to treat OIC in adults with chronic non-cancer pain was based primarily on data from 2 replicate multicenter, randomized, double-blind, placebo-controlled clinical trials, each with a 12-week treatment and evaluation period. The database used	The effectiveness of naldemedine for treatment of OIC in patients with chronic, non-cancer pain was demonstrated in adequate and well-controlled clinical trials. The eligibility criteria were considered appropriate to ensure a study population sufficiently representative of the target patient population and the interpretability of efficacy assessments. In addition, the primary endpoint was considered an appropriate measure of a clinically meaningful treatment benefit upon which to base efficacy assessments. Additional evidence of naldemedine efficacy was provided by secondary endpoint data. Although the clinical significance of data for each individual secondary endpoint as a

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	as the primary source for efficacy analyses included 1095 subjects with OIC based on pre-specified diagnostic criteria (refer to Section 6.1.1) and ≥4 weeks of opioid use with a stable dosage regimen, who were randomized 1:1 to receive either naldemedine 0.2 mg once daily (n=549) or matching placebo (n=546). The designated primary endpoint was the difference in proportion of responders between groups, using a responder definition designed to assess treatment effect independent of rescue laxative use (i.e., SBM events) and over the entire treatment period (refer to Section 6.1.1). The proportion of responders was higher among naldemedine-treated patients than placebo-treated patients, achieving statistical significance for both trials (p=0.002 and <0.0001). Sensitivity analyses of primary endpoint data yielded comparable results, thus demonstrating the robustness of primary efficacy results. Furthermore, statistically significant treatment differences were demonstrated for all 4 key pre-specified secondary endpoints in both pivotal trials, each comparing the mean change in weekly frequency from baseline for one of the following specified bowel movement events—(1) change in the frequency of SBMs per week from baseline to the last 2 weeks of the treatment period, (2) change in the frequency of SBMs per week from baseline to Week 1 of treatment, (3) change in the frequency of CSBMs per week from baseline to the last 2 weeks of the treatment period, and (4) change in the frequency of SBMs without straining per week from baseline to the last 2 weeks of the treatment period.	standalone indicator of treatment benefit could not be established, consistent results demonstrating statistical superiority of naldemedine vs. placebo for all 4 endpoints in both clinical trials was considered supportive of the primary efficacy data.
Risk	The naldemedine safety population consists of 1163 subjects with chronic, non-cancer pain who received ≥1 dose of naldemedine in phase 3 clinical	The safety profile was generally comparable to the known safety profile of other PAMORA

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	trials, as well as a similar population of placebo-treated subjects (total 2328 subjects). The primary sources of safety data included the two 12-week studies, as well as a long-term, dedicated safety trial with a planned 52-week treatment period. As with other PAMORAs, Gastrointestinal (GI) events represented the majority of adverse reactions associated with naldemedine treatment (i.e., events reasonably attributable to treatment). 236 of 1163 (10.3%) naldemedine-treated subjects experienced ≥ 1 of the 4 major GI reactions (abdominal pain, diarrhea, nausea, and vomiting), of which >50% reported onset of symptoms within the first 7 days of treatment (n=122, 10.4), and >30% reported onset on day 1 (n=71, 6.1%). The most common ARs were abdominal pain and diarrhea, occurring in 10.4% and 8.9% of naldemedine-treated subjects (vs. 4.5% and 3.4% of placebo), respectively. GI adverse reactions led to early study discontinuation in 38 naldemedine subjects (3.3%). However, SAEs for GI reactions were rare (n=6 naldemedine subjects), and 3/6 of subjects subsequently completed treatment. Forty-six cases of opioid withdrawal were identified either by investigator report or retrospective chart review—31 in naldemedine patients vs. 15 in placebo patients. No significant difference in pain (either pain scores or AEs) between groups was determined; however, methodology was not adequate for conclusive assessments. Regarding other labelled class-wide safety concerns, 1 case of hypersensitivity was reported and resulted in hospitalization and treatment discontinuation. No gastrointestinal perforations occurred, although 2 naldemedine subjects were diagnosed with gastric ulcerations (vs. 0	medications approved for treatment of OIC. GI reactions comprised the majority of ARs, and led to study discontinuation in 5% of all naldemedine-treated subjects (30% of subjects experiencing GI ARs.) However, serious events were rare and symptoms resolved without sequelae upon treatment discontinuation, and some subjects had spontaneous resolution despite ongoing treatment. Therefore, these reactions appear to be more of a tolerability issue, rather than a severe safety issue. The naldemedine safety evaluation did not identify any new or unexpected safety signals or serious reactions, including risk of MACE, attributable to treatment. The naldemedine safety database represents the largest prospective collected dataset of randomized, double-blind treatment to date among the PAMORAs. Safety assessments for all phase 3 trials included prospective identification and adjudication of MACE. Although the safety data did not demonstrate an increased frequency of MACE compared to placebo, the safety database from controlled phase 3 trials of naldemedine was too small to generate to yield an event frequency high

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Risk Management</u>	placebo subjects). This application also included results of specific safety assessments to assess the risk of major adverse cardiac events (MACE), including prospective adjudication by an independent committee, in order to address a class-wide safety concern arising from the long-term safety trial alvimopan (Entereg), a PAMORA not indicated for OIC and approved only for short-term use. An increased frequency of MACE compared to placebo was not observed in phase 3 trials [5 adjudicated MACE cases in the naldemedine arm (vs. 6 in placebo; RR 0.835, 95% CI 0.256, 2.728), and 8 cases when all sudden cardiopulmonary deaths and 1 un-adjudicated myocardial infarction are included (vs. 7 in placebo; RR 1.145, 95% CI 0.418, 3.137). The primary molecular and physiologic considerations relevant to PAMORA toxicity are off-target binding of opioid receptors (all subtypes) and the potential for CNS penetration, particularly in patients with disruptions of the BBB. Unlike exogenous opioids, opioid receptor binding by naldemedine and other opioid antagonists is not restricted to the mu (μ) subclass of opioid receptors, though relative binding and degree of agonist/antagonist activity of the receptor subtypes [μ (μ), delta (δ), and kappa (κ)] vary among PAMORAs. Product labeling will address the safety concerns of naldemedine and other PAMORAs, including class-wide warnings and precautions. Though not observed in clinical trials of naldemedine, this includes a warning of gastrointestinal perforation. Product labeling for the PAMORAs indicated for OIC, including	enough to statistically rule out an increased risk of MACE with naldemedine treatment.
	Overall, clinical trial data support the finding of a favorable benefit-risk profile for naldemedine. The product labeling adequately reflects the overall safety profile of naldemedine and class-	

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	naldemedine, does not include safety information specific to risk of MACE. However, the concern for an increased risk of MACE with these products has not been resolved and postmarketing evaluations for currently approved products are ongoing. A PMR to obtain similar postmarketing data for naldemedine will be issued. Post-approval Studies and Trials: Post-approval, the Applicant will conduct an epidemiological study to assess for increased risk of MACE, a requirement that has been previously issued to other PAMORAs approved for treatment of OIC.	wide safety concerns for PAMORAs approved for treatment of OIC. Because a class-wide risk of increased MACE has not been established, relevant safety information has not been included in the labeling for PAMORAs approved for OIC. However, postmarketing data are still needed to adequately address this concern.

2 Therapeutic Context

Analysis of Condition

Opioid analgesics represent one of the most prescribed classes of medications worldwide and are commonly prescribed for the management of moderate to severe chronic pain. The estimated prevalence of chronic pain is 15% in the adult US population, and approximately one-third are prescribed opioid analgesics. [6] Reports estimate that more than 3% of American adults are undergoing opioid therapy for more than 3 months for chronic noncancer pain.[1] OIC is the most frequent opioid side effect, affecting at least 40% of opioid-treated patients[4] Unlike other opioid side effects, such as sedation and respiratory depression, patients typically do not develop tolerance to the gastrointestinal side effects of opioids with prolonged exposure. Instead, OIC typically persists with ongoing opioid treatment and progressively worsens with increased opioid doses, often despite aggressive treatment with laxatives and stool softeners.[3]

Common symptoms of OIC include abdominal pain, cramping, and bloating pain, lumpy or hard stools, sensation of incomplete evacuation, and sensation of anorectal obstruction.[6] Although life-threatening complications are rare, OIC has many significant and clinically important sequelae that negatively impact patients' quality of life, including anorexia, poor nutrition, fecal impaction, fecal incontinence, pseudo-obstruction, impaired drug absorption, and urine retention. In addition, OIC can be a dose-limiting side effect and lead to inadequate pain management. [4,5]

Opioid receptors, predominantly μ sub-type, are densely distributed throughout the myenteric plexus and submucosal plexus of the stomach, small intestine, and large intestine and are involved in several neural pathways responsible for GI motility and secretion of fluid and electrolytes. Activation of μ -opioid receptors disrupts the coordinated, peristaltic contractions of the GI tract, causing delayed gastric emptying and slowed intestinal transit. In addition, μ -opioid receptor activation decreases stool water content by decreasing secretion of water and electrolyte into the gut lumen and increasing fluid absorption from the colon. Furthermore, opioids increase ileocecal and anal sphincter tone and impair the defecation reflex through reduced sensitivity to distension and increased internal anal sphincter tone. [5]

2.2. Analysis of Current Treatment Options

Currently, there are three approved drugs for the treatment of OIC, two of which are in the class of peripherally-acting opioid receptor antagonists (PAMORAs)—Relistor (methylnaltrexone bromide), available as a subcutaneous injection and oral tablet, and Movantik (naloxegol), an oral tablet for oral administration. The third approved drug for OIC is

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Amitiza (lubiprostone), a chloride channel activator that is also approved for the treatment of chronic idiopathic constipation (CIC) and irritable bowel syndrome (IBS). These FDA-approved drugs for treatment of OIC are listed in Table 1.

Table 1: Approved Drugs for Opioid-Induced Constipation (OIC)

Drug	Drug Class	FDA Approval	Route/ Dosage Form	OIC-Related Indication
Relistor (methylnaltrexone) NDA 21964/208271	PAMORA	24 April 2008 (NDA 21964)	Subcutaneous injection	OIC in adults with advanced illness who are receiving palliative care when response to laxatives has not been sufficient
		19 July 2016 (NDA 208271)	Oral tablet	OIC in adults with chronic, non-cancer pain
Amitiza (lubiprostone) NDA 21908	Chloride channel activator	31 January 2006 (OIC: 19 April 2013*)	Oral capsule	OIC in adults with chronic, non-cancer pain
Movantik (naloxegol) NDA 204760	PAMORA	16 September 2014	Oral tablet	OIC in adults with chronic, non-cancer pain

(Source: Reviewer's Table)

Abbreviations used in table: PAMORA, peripherally-acting μ (mu)-opioid receptor antagonist

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Naldemedine is a new molecular entity (NME) and is not currently marketed in the U.S.

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3.2. Summary of Presubmission/Submission Regulatory Activity

A summary of key presubmission regulatory history of naldemedine is presented in Table 2.

Table 2: Key Pre-submission Regulatory Activity for NDA 208854

Date	Type of Activity	Important Regulatory Activity/Action(s) (if Applicable)
05 December 2008	Development International Birth Date (Japan)	
29 March 2010	Submission- Investigational New Drug (IND) Application	
17 November 2011	Special Protocol Assessment- Carcinogenicity Study	FDA agreement with proposed 2-year oral carcinogenicity studies in rats and mice (Executive CAC c with proposed doses for both rat and mouse studies (0, 10, 30, and 100 mg/kg/day), based on expected exposure at highest dose of AUC>25 times the AUC in humans at the proposed dose, but noted that the study may not be acceptable if the clinical dose changes such that the AUC in the carcinogenicity studies is no longer $\geq$ 25-fold higher than human exposures with treatment)
28 December 2012	Submission of Thorough QT Study Protocol	Reviewed by the QT Studies Interdisciplinary Review Team (IRT); study design deemed adequate
19 February 2013	Type B/End of Phase 2 Meeting	<u>Purpose:</u> Discussion of naldemedine phase 3 clinical development program and general plan for NDA filing <u>Key discussion points:</u> Phase 3 clinical trial design, including: • Concurrence with proposed 12-week efficacy assessment period • Definition of “Responder” for primary endpoint as weekly response for $\geq$9/12 weeks, and response for 3 or the last 4 weeks of the 12-week study period • Minimum of 4 days of diary entries in a week for the week’s data to be considered evaluable with <4 days of diary entries treated as “non-responder” for that week • Rescue laxative use/prohibited concomitant medications • Proposed treatment arms (naldemedine 0.2 mg vs. placebo) & randomization scheme (1:1) with

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Date	Type of Activity	Important Regulatory Activity/Action(s) (if Applicable)
		stratification by opioid dosage • Sample size calculation • Handling of missing data (FDA disagreement with proposed conservative approach for primary endpoint analyses with: 4 ITT population (i.e., all randomized subjects) as primary analysis population 5 Pre-specified sensitivity analyses to evaluate the impact of missing data 6 Subjects with inadequate primary endpoint data treated as “nonresponders” 7 Use of model-based multiple imputation • Required safety database to adequately address MACE risk, understanding that sample size adequacy (i.e., hazard ratio of 2) depends on the number of events, not the number of subjects/extent of exposure • Justification for dose selection for phase 3 clinical trials required for each patient population • Agreement with plan to limit proposed treatment indication to adults with chronic non-cancer pain • PK data needed to support NDA, including PK profiles for the to-be-marketed formulation • Agency disagreement with proposal
10 April 2013	Submission of initial PSP (iPSP) with request for full waiver of pediatric studies	
17 July 2013	Presentation of initial PSP to Pediatric Review Committee (PeRC)	PerRC concurrence with Applicant’s request for full waiver of pediatric studies in iPSP (see note) Communication with the Applicant that a Request for Waiver from all PREA requirements should be submitted at the time of naldemedine NDA submission (letter to Sponsor sent on 21 January 2014)
11-12 June 2014	Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)	Meeting with advisory committee, FDA, and industry to discuss potential cardiovascular risks associated with the class of peripherally-acting mu-opioid receptor antagonists and long-term safety assessments to evaluate these risks
18 September 2014	Type C Meeting	Purpose: Discussion of the safety data for submission in the naldemedine NDA, particularly with

Date	Type of Activity	Important Regulatory Activity/Action(s) (if Applicable)
		respect to the Applicant’s proposed 52-week phase 3 safety trial (Study V9235) Key discussion points: • Use of the standardized definition of Major Adverse Cardiac Events (MACE) – composite of nonfatal MI, nonfatal stroke, and CV death • Agreement to proposed change of primary endpoint for Study V9235 from MACE to general safety of naldemedine • Completion of Study V9235 required prior to NDA submission with submission of complete safety dataset in NDA • Agreement with plan to conduct analyses of naldemedine effect on analgesic efficacy and opioid withdrawal using the following assessments/tools (input from DAAAAP): (1) 11-point Numeric Rating Scale (NRS) (2) Mean weekly average opioid use (maintenance and breakthrough), expressed in morphine equivalent doses (3) Clinical Opiate Withdrawal Score (COWS) (4) Subjective Opiate Withdrawal Score (SOWS)
11 February 2015	Type C Meeting	<u>Purpose:</u> To obtain concurrence on the overall safety package to support an NDA Key discussion points: Disagreement that the available data from Japanese clinical trials of patients with cancer pain would be sufficient to support an indication due to insufficient data to demonstrate duration of response and to justify dosing; also, demonstration of applicability of data in Japanese population to the US population would be needed Requirement to address the abuse potential of naldemedine—the Agency advised the Applicant to conduct 3 nonclinical studies and assess abuse related signals or adverse events in all clinical studies (input from CSS)
19 March 2015	Submission of protocols for abuse-related animal studies	Reviewed by CSS and feedback sent to the Applicant 13 May 2015
03 August 2015	Submission of Proprietary Name Request	Determination that the proposed proprietary name (Symproic) is acceptable based on reviews by DMEPA Proprietary Name Granted letter sent (dated 07 December 2015) communicating that the

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Date	Type of Activity	Important Regulatory Activity/Action(s) (if Applicable)
30 September 2015	Type B/Pre-NDA Meeting	proprietary name is considered conditionally acceptable and a formal request for proprietary name review is required once NDA is submitted <u>Purpose:</u> Discussion of planned naldemedine NDA submission Key discussion points: • Agreement with Applicant’s proposal to submit interim analyses from the ongoing safety trial (Study V9235) with the NDA (i.e., “Core Period Data Set”) with later submission of a “Supplemental Period Data set” for the subjects with ongoing treatment at data cutoff for the “Core Period” • Adequacy of the thorough abuse potential assessment cannot be determined until completion of the animal abuse liability studies and the component of the abuse potential evaluation required for NDA submission • Agency disagreement with Applicant’s proposed [REDACTED] (b) (4)

(Source: Reviewer’s Table)

Abbreviations used in table: CSS, controlled substance staff; DAAAAP, Division of Anesthesia, Analgesia, and Addiction Products; DMEPA, Division of Medication Error Prevention and Analysis; DPMH, Division of Pediatric and Maternal Health; LOCF, last observed carried forward; MACE, major adverse cardiac events; MI, myocardial infarction; PeRC, Pediatric Review Committee; PK, pharmacokinetics; PMHS, Pediatric and Maternal Health Service; PSP, pediatric study plan

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Regulatory History- Pediatric Study Plan

Pediatric Studies in OIC:

The proposed indication for treatment of OIC in patients with chronic, non-cancer pain has been included in the FDA list of “adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics” because studies would be impossible or highly impractical.

This qualification is based primarily on the Agency’s determination that extrapolation of adult clinical trial data would not be sufficient to establish efficacy of OIC treatments in children, and pediatric studies with ≥ 4 weeks of concomitant study drug/opioid treatment would be required to adequately assess treatment effect. However, an FDA working group assembled specifically to assess opioid usage in children failed to identify a population of pediatric patients who are likely to (1) be treated with chronic, round-the-clock opioid therapy; (2) develop constipation as a sequela of opioid use that is unresponsive to dietary modifications; (3) and require sustained opioid dosages of for ≥ 4 weeks during study participation.

(b) (4)

Consequently, the Agency has reached consensus that pediatric trials for OIC in chronic non-cancer pain are considered highly impracticable due to the low numbers of patients, and “OIC in chronic, non-cancer pain” has been listed among the PeRC-accepted “adult-related conditions that qualify for a waiver because they rarely or never occur in pediatrics.”

For additional details, refer to the DPMH memo by Ethan Hausman submitted on 18 September 2015 under IND 107475.

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This NDA submission includes a formal request for a full waiver of pediatric studies of naldemedine under the Pediatric Research Equity Act (PREA). The full waiver request is consistent with the pediatric plan submitted by the Applicant on 10 April 2013 and agreed upon by the Pediatric Review Committee (PeRC) on 17 July 2013, consistent with other pediatric study plans for OIC in patients with chronic non-cancer pain.

However, the Applicant’s pediatric plan did not remain consistent during the period of drug development between End-of-Phase 2 (EOP2) and NDA submission. In the background materials for both the EOP2 and pre-NDA meetings, the Applicant indicated (b) (4)

The following is a brief chronological summary of the regulatory actions and advice related to the naldemedine pediatric plan.

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- 19 February, 2013: EOP2 meeting- The Applicant requested Agency feedback regarding (b) (4)

- 10 April 2013: Pediatric plan submission- The Applicant submitted a plan to request full waiver of pediatric studies Pediatric Research Equity Act (PREA), on the basis that pediatric studies would be impossible or highly impractical due to the small number of available patients
- 17 July 2013: PeRC meeting- presentation of naldemedine pediatric study plan and agreement for full waiver of pediatric studies under PREA
- 21 January 2014: Correspondence letter sent by the Agency communicating agreement with the plan for request of a full waiver of pediatric studies with request for submission of a written response within 90 days of the letter to communicate their agreement or disagreement with the Agency's understanding of the pediatric study plan. (Note: the Applicant did not submit a written response to the Agency.)
- September 2015: Pre-NDA meeting discussion- In the meeting background materials, the Applicant described (b) (4)
(b) (4)
- 23 March 2016: Submission of a formal request for full waiver of pediatric studies, along with NDA submission
- 2016: Request sent by the Agency for submission of an "Agreed Initial Pediatric Study Plan" document, as requested in the correspondence sent on January 21, 2014

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- 09 May 2016: Submission of the “Agreed Initial Pediatric Study Plan” and agreement letter was sent to the Applicant.

Presubmission Regulatory History-Cardiovascular Risk Assessment

During the EOP2 Meeting on 19 February 2013, the Division communicated that a cardiovascular outcomes trial (CVOT) would be needed to be conducted prior to approval to assess for an increased risk of major adverse cardiac events (MACE) with chronic naldemedine administration. The basis for the Division’s concern was the identification of a possible cardiovascular safety signal (MACE) during clinical trials of other members of the drug class of peripheral opioid receptor antagonists. The Division also noted that naldemedine antagonizes opioid receptor subtypes (e.g., δ -delta) that are known to be present in the cardiovascular system and that are implicated in cardioprotection. Therefore, the Division stated that the naldemedine CVOT should be designed to include an adequate number of events to perform these safety assessments, and sample size determinations should account for the incidence of MACE and exposure required for the safety dataset, rather than just the number of patients.

To address the need for cardiovascular assessments across the class of peripheral opioid receptor antagonists, a meeting of the Anesthetic and Analgesic Drug Products Advisory Committee was held on 11-12 June 2014. Among the FDA presenters was Dr. Clara Kim (Office of Biostatistics/Division of Biometrics) who spoke about statistical considerations in the design of randomized controlled cardiovascular outcomes trials.

Based on the AC discussions, a post-marketing requirement (PMR) was issued to conduct an observational epidemiologic study of Movantik (naloxegol), for which the clinical development program had been completed and the marketing application was under review at the time of the AC meeting. This PMR has a deadline of June 2018 for interim report submission and December 2023 for final clinical study report submission.

For naldemedine, the Applicant proposed to conduct a pre-approval, long-term (52-week), randomized, placebo-controlled safety trial (Study 1326V9235). A Type C Meeting was held on 18 September 2014 at the request of the Applicant to obtain feedback regarding the design of Study 1326V9235, as well as the adequacy of the overall safety database to support the registration of naldemedine for treatment of OIC. Although Study 1326V9235 was initially intended as a CVOT for assessment of MACE, the primary endpoint was changed to the general safety of naldemedine, with a proposed population size of 1200 subjects (600 randomized to each arm), for which they specified an assumption of a 15% drop-out rate. (This represented a reduction from the original plan to enroll 1500 subjects.) In response, the Division noted that, historically, drop-out rates in long-term safety studies for OIC with chronic non-cancer pain were >30%, and although the sample size was not determined using a specific power calculation, the Division recommended that the Applicant account for a higher number of dropouts than their predicted 15% rate to ensure adequate naldemedine exposure for safety assessments.

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The Division of Biometrics VII stated that the proposed trial, Study 1326V9235, to assess cardiovascular risks of naldemedine was not designed to test a statistical hypothesis, and therefore was not statistically powered. The sponsor proposed to summarize the primary endpoint by the proportion of MACE and the corresponding 95% confidence interval (CI) by treatment group. Because this study was considered to be descriptive in nature, the safety biostatistics reviewers did not provide specific comments for the Division or feedback for the Applicant regarding the trial design or size of the proposed study population. (see memo by Ling Lan and Clara Kim dated 29 September 2014)

The issue of adequacy of the safety database for NDA submission to support the registration of naldemedine was addressed again during the pre-NDA meeting on 30 September 2015. The Applicant proposed NDA submission with an interim dataset for Study V9235. During discussions with the Applicant, the Division agreed to NDA submission prior to completion of Study V9235 with a “Core Period Data Set” to be included in the NDA submission, and a “Supplemental Period Data Set” to be submitted in the 120-Day Safety Update (see below). The Division stated that the adequacy of the available data to assess the safety of naldemedine would be evaluated as part of the review process and cautioned the Applicant that submission of insufficient safety data in the NDA could result in a review clock extension.

Data Sets for Study V9235, as agreed upon during Pre-NDA Meeting (30 September 2015):

- *Core Period Data Set: to consist of data for all randomized subjects, up to the cutoff date of June 24, 2015, at which time subjects should have completed between 24 and up to 52 weeks of treatment exposure, and will serve as the primary dataset for safety analyses in the Study V9235 Clinical Study Report (CSR) for NDA submission.*
- *Supplemental Period Data Set: to consist of remaining data (i.e. study visits not completed at the time of the Core Period Data Set cutoff) for supplemental safety data to be submitted with the Day-120 safety update report.*

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical inspections were conducted at 6 sites, 3 sites who participated in Study V9231 and 3 sites for Study V9232. The sites selected for inspection had not had a recent OSI investigation, were among the sites with highest enrollment, and may have been identified as having efficacy results inconsistent with the overall population data or disproportionate large or small number of reported protocol violations. The sites inspected had enrollment between 14 and 26

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subjects. For additional details, the reader is referred to the summary review by Susan Susan Leibenhaut, M.D., dated 22 December 2016.

None of the clinical site inspections identified findings likely to have negatively impacted the integrity of the clinical trial data. Four clinical sites were classified as No Action Indication (NAI), and 2 clinical sites were classified as voluntary action indication (VAI). None of the violations cited were considered to have an impact on data integrity. The reviewer concluded that the studies have been conducted adequately, and the data generated by the studies appear acceptable.

4.2. Product Quality

According to the CMC review team, the applicant provided sufficient data to assure the identity, strength, purity, and quality of the drug product. At the time of this review, there were no ongoing issues regarding product quality. In addition, the Office of Process and Facilities (OPF) recommended "Approval" recommendation for the facilities involved in this application as of this review. The reader is referred to the full CMC review by Joseph Leginus (primary drug substance reviewer) and Sarah Ibrahim (primary drug product review) for a detailed evaluation of product quality.

Naldemedine tosylate is a white to light tan powder, soluble in dimethylsulfoxide and methanol, slightly soluble in alcohol and water. Naldemedine tablets for oral use contain 0.26 mg of naldemedine tosylate equivalent to 0.2 mg naldemedine (S-297995), the primary active moiety. Excipients are D-mannitol, croscarmellose sodium, magnesium stearate, hypromellose, talc, and yellow ferric oxide. Naldemedine tablets are unscored.

4.3. Clinical Microbiology

A clinical microbiology evaluation was not indicated for this product.

4.4. Nonclinical Pharmacology/Toxicology

The reader is referred to the nonclinical review by Tracy Behrsing, Ph.D., dated 21 November 2016 for a full discussion of naldemedine nonclinical study data submitted in support of this application. The following is a summary of important findings from the nonclinical program, with particular attention to information to be included in product labeling:

- Toxicology: Repeat-dose toxicity studies with naldemedine were conducted in multiple species, with durations of up to 6 months in rats and 9 months in dogs. In the 6-month rat study, systemic exposures (AUC) at the NOAEL (100 mg/kg/day) were approximately 3600 times that in humans at the recommended human dose.

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- The liver was the primary target organ of toxicity in repeat dose studies. At doses much higher than the recommended human dose, elevated transaminases and histopathological changes of centrilobular necrosis were observed.
- In the 9-month study in dogs, systemic exposures (AUC) at the NOAEL (4 mg/kg/day) were approximately 345 times that in humans at the recommended human dose. In 1-month toxicity studies in rats, prolongation of diestrus occurred at doses as low as 0.3 mg/kg/day. While a NOEL for this effect (which may be related to treatment-related increases in prolactin) was not identified, recovery of the estrous cycle generally occurred even during the dosing period. No significant gross pathological findings.
- Distribution: In a study of drug distribution with radiolabeled naldemedine, penetration across the blood brain barrier into the CNS was not observed.
- Carcinogenesis: The carcinogenic potential of naldemedine was evaluated in 2 studies—a 2-year in mice and a 2-year study in rat using naldemedine doses up to 100 mg/kg/day, for which exposures were approximately 17,500 and 6,300 times the human exposures (AUC) at the recommended human dose in mice and rats, respectively. No evidence of carcinogenic potential was observed in either of these studies.
- Mutagenesis: Naldemedine was not genotoxic in a bacterial reverse mutation (Ames) assay, a chromosomal aberration assay with cultured Chinese hamster lung cells, and an in vivo rat bone marrow micronucleus assay.
- Fertility/embryofetal development: A species-specific prolongation of diestrus phase was noted in rats at a dose of 10 mg/kg/day in female rats (AUC approximately 180 times the AUC in humans at the recommended human dose). Overall, no effects on fertility or reproductive performance were observed in either male or female rats at oral doses up to 1000 mg/kg/day (approximately 17,000 times the human exposures (AUC) at the recommended human dose). In embryo-fetal development studies, increased abortion/premature deliveries were observed in rabbits treated with 400 mg/kg/day (844 times the human AUC at the recommended human dose). These events were attributed to marked decreases in maternal food consumption and lower fetal body weights. In rats, no adverse effects on embryo or fetal development were observed with doses up to 1000 mg/kg/day. In the pre- and postnatal development study in rats given naldemedine during the postimplantation through weaning at the dose up to 1000 mg/kg/day, one dam died at parturition at 1000 mg/kg/day and poor nursing; decrease in body weight gain and decrease in food consumption were noted at 30 and 1000 mg/kg/day. Decreases in the viability index on Day 4 after birth were noted at 30 and 1000 mg/kg/day, and low body weights and delayed pinna unfolding in pups were noted at 1000 mg/kg/day. The AUC_{0-24hr} at 30 mg/kg/day was 626 times the human AUC_{0-τ} at the recommended human dose. No adverse effect level on pre- and postnatal

development including maternal function such as maintenance of pregnancy, delivery, and nursing was observed at 1 mg/kg/day, which is 12 times the AUC_{0-τ} at the recommended human dose.

- At the recommended dose, the proposed specifications for actual and potential impurities and residual solvents comply with limits set by the ICH Q3A guidelines. In addition, the quantities of these compounds detected during batch testing were below the specified limits. Actual and potential impurities formed during the manufacturing process were evaluated for mutagenic potential, and 1 of the 6 impurities (b) (4) was shown to test positive for bacterial mutagenicity.
- In vitro pharmacology: The reported binding affinities of naldemedine for human mu, delta, and kappa opioid receptors (expressed as K_i values) were 0.34, 0.43, and 0.94 nM, respectively. Relative to naldemedine, each of the metabolites studied were less potent or had no binding affinities for mu, delta, and kappa receptors, with the exception of naldemedine 6-O-β-D-glucuronide, which had a K_i value of 0.51 nM for the delta receptors subtype. The parent compound has antagonist properties/activity at all subtypes. While nornaldemedine (a major metabolite in humans) showed weak agonistic activity for delta receptors, the EC₅₀ value was approximately 340 times the human C_{max} for this metabolite at the recommended human dose of 0.2 mg once daily.
- Primary pharmacology (rats): naldemedine prevented morphine- and oxycodone-induced suppression of small intestinal transit (ED₅₀ values of 0.02 – 0.23 mg/kg) and antagonized the inhibitory effect of morphine on castor oil-induced diarrhea (ED₅₀ value of 0.01 mg/kg).

4.5. Clinical Pharmacology

The dose-response and exposure-response data from naldemedine clinical trials were considered adequate to support the effectiveness of the proposed naldemedine dose and dosing regimen to treat OIC in patients with chronic, non-cancer pain. In addition, adequate data were available to determine appropriate dosing in special populations and evaluate drug-drug interactions. The following is a summary of the Clinical Pharmacology findings to support dosing and labeling recommendations for naldemedine. The reader is referred to the full Clinical Pharmacology review by Sandhya Apparaju for greater detail.

Preliminary evidence of effectiveness, proof-of-concept, and dose-range guidance for phase 3 naldemedine clinical trials in the proposed population was obtained from a randomized, double-blind, placebo-controlled, parallel-group, phase 2b dose-ranging study (Study V9221) that evaluated 3 dosages of naldemedine (0.1 mg, 0.2 mg and 0.4 mg once daily for 28 days) in a population of subjects with OIC and chronic non-cancer pain. Efficacy (change in the frequency of SBMs per week from baseline to the last 2 weeks of the treatment period) was

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evaluated. Mean changes from baseline in SBMs per week relative to placebo were significantly different for the 0.2 mg and 0.4 mg doses (increase of 3.38 and 3.63 SBMs per week vs. 1.42 in placebo) but not for the 0.1 mg dose (increase of 1.99 SBMs per week). The efficacy at the two higher doses was comparable (not significantly different), but significantly different from the 0.1 mg group. Similar trends were noted for the key secondary endpoints including the mean change in the frequency of SBMs from baseline to Weeks 1, 2, 3 and 4 of the trial, the change from baseline in the frequency of complete spontaneous bowel movements (CSBMs), the proportion of SBM responders during the last 2 weeks of the treatment period and the time to first spontaneous bowel movement after the initial administration of study drug. Data for these secondary endpoints support significant but comparable efficacy at the 0.2 mg and 0.4 mg doses, and a modest but not statistically significant effect at the 0.1 mg dose of naldemedine. Overall, the dose-response for primary and secondary efficacy outcomes in this trial provided supportive evidence of effectiveness of the 0.2 mg dose of naldemedine.

4.5.1. Mechanism of Action

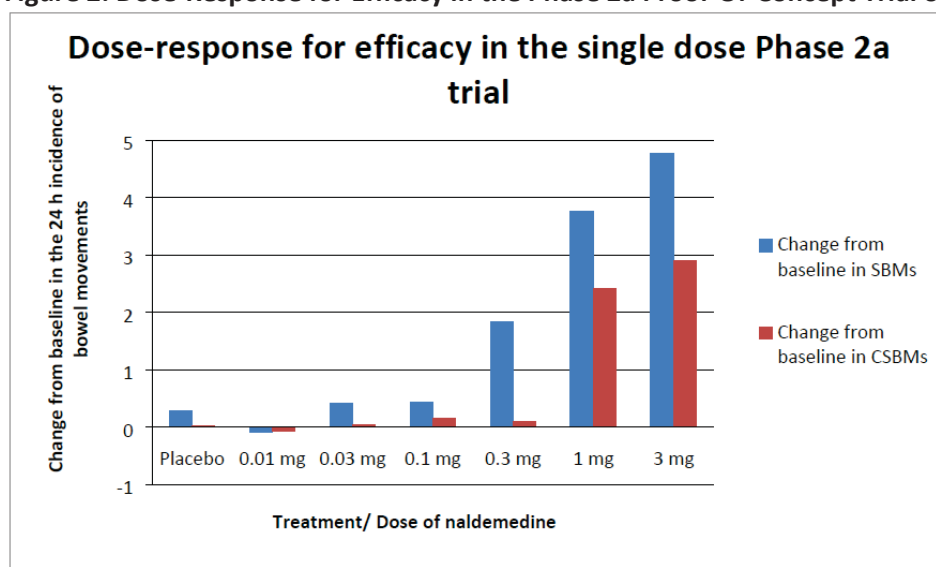
Naldemedine is a naltrexone derivative, with a large polar surface area that reduces its ability to access the central nervous system. It acts as a peripherally-acting μ -opioid receptor antagonist (PAMORA) and blunts the effect of opioid drugs at their peripheral receptors, in particular the enteric nervous system in the GI tract. In this way naldemedine reverses the constipating effects of opioids, thereby improving bowel movements, stool consistency and reducing straining.

4.5.2. Pharmacodynamics

In single-ascending dose studies, naldemedine was well tolerated at up to 100 mg. Doses up to 30 mg for 10 days were also well tolerated in multiple ascending dose trials. However, it is important to note that these studies were conducted in healthy individuals without concomitant opioid treatment and sustained opioid exposure prior to treatment with naldemedine. The tolerability profile of opioid receptor antagonism by naldemedine would be expected to differ in individuals with chronic opioid exposure.

In the phase 2a, single dose, proof of concept trial, naldemedine was administered over a 300-fold dose range (0.01 mg to 3 mg). A dose-related increase in SBMs during the 24 hours following a single dose of naldemedine was observed, particularly at 0.3 mg or higher doses (Figure 3). The proportion of subjects who reported a GI-related TEAE increased in a dose-dependent manner, with an increase in frequency observed beginning at a dose of 0.3 mg or higher. Based on these data, doses of 0.1 mg, 0.2 mg, and 0.4 mg were selected for the Phase 2b trial. Although the clinical efficacy after a single dose of 0.1 mg was not robust or statistically significant in this trial, this dose was included because it was well-tolerated and the potential for additional efficacy after multiple daily doses was of interest.

Figure 2: Dose-Response for Efficacy in the Phase 2a Proof-Of-Concept Trial of Naldemedine



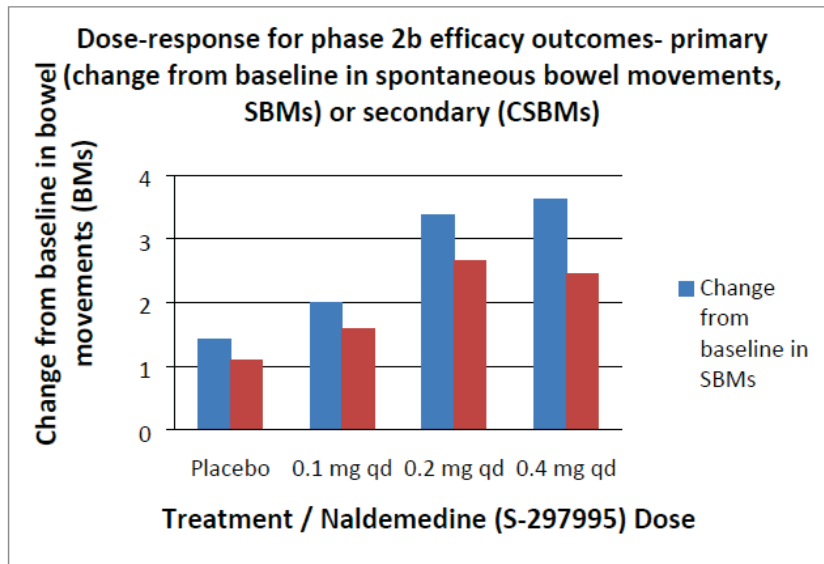
(Source: Figure 4, Clinical Pharmacology Review for NDA 208854 by Dr. Sandhya Apparaju, page 14/84)
Abbreviations used in figure: CSBM, mg, SBM

In the phase 2 dose-ranging trial, all tested doses of naldemedine (0.1 mg, 0.2 mg, and 0.4 mg) were associated with an increase in SBM frequency from baseline that was greater than placebo, but results for the 0.1 mg dose did not achieve statistical significance (Figure 4). No additional benefit was noted at the 0.4 mg dose (compared to the 0.2 mg dose), and this higher dose was associated with a higher adverse event (AE) rate (Figure 6). Similar differences in

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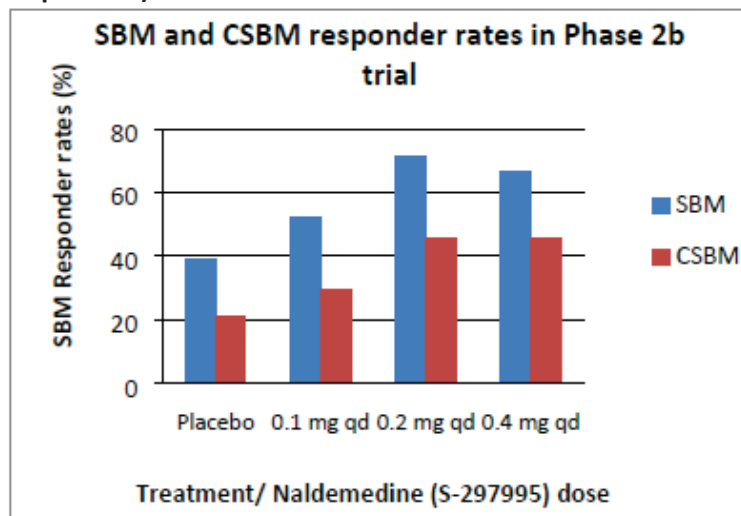
dose-response were observed for dose-group SBM responder rates, as defined for the phase 3 primary efficacy endpoint (Figure 5). Based on these data, phase 3 trials were designed using only the 0.2 mg dose.

Figure 3: Dose-Response for Efficacy Outcomes in the Phase 2b Dose-Ranging Trial (Change in SBM Frequency from Baseline)



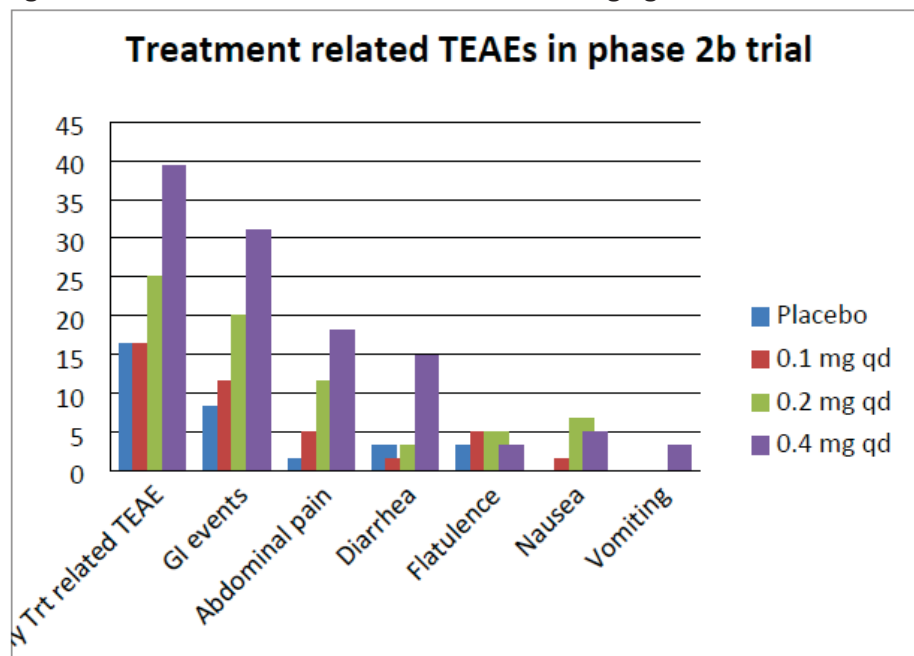
(Source: Figure 3, Clinical Pharmacology Review for NDA 208854 by Dr. Sandhya Apparaju, page 13/84)

Figure 4: Dose-Response for Efficacy Outcomes in the Phase 2b Dose-Ranging Trial (Proportion of Responders)



(Source: Figure 4, Clinical Pharmacology Review for NDA 208854 by Dr. Sandhya Apparaju, page 14/84)

Figure 5: Dose-AE Trends in the Phase 2 Dose-Ranging Clinical Trial for Naldemedine



(Source: Figure 6, Clinical Pharmacology Review for NDA 208854 by Dr. Sandhya Apparaju, page 15/84)

The Clinical Pharmacology reviewer concluded that the dose and exposure response relationships for safety (i.e. gastrointestinal disorders, abdominal pain, and diarrhea) suggest that the 0.2 mg dose is acceptable.

4.5.3. Pharmacokinetics

Summary of ADME PK Results

Naldemedine PK parameters were comparable in healthy volunteers and OIC patients.

Naldemedine exposures (C_{max} and AUC) increased in a nearly dose proportional manner following single and multiple daily doses. Steady-state was reached within two days and a modest accumulation was noted in healthy, and accumulation in OIC patients was minimal.

PK variability in healthy volunteers was small to moderate across the various parameters (14 % to 25 %), while it was somewhat higher in OIC patients in the phase 2b trial (22 % - 48 %).

Naldemedine was not removed by dialysis. The fraction of naldemedine bound to human serum proteins is 93.2% to 94.2%, primarily to albumin. There is no concentration-dependence of the protein binding in the range from 0.02 to 2 $\mu\text{g/mL}$. Naldemedine has a terminal elimination $T_{1/2}$ of ~ 9 to 11 hours.

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Naldemedine is primarily metabolized by CYP3A4 to form nor-naldemedine, with some contribution by UGT1A3 to form both naldemedine 3-glucuronide (3-G) and naldemedine 6-G. Naldemedine and major metabolite (nor-naldemedine) do not cause clinically relevant induction or inhibition of major CYP450 enzymes.

Naldemedine is also a sensitive substrate of p-glycoprotein (p-gp). No relevant inhibition of major transporters was noted. (See drug-drug interactions below)

Naldemedine is absorbed with a median T_{max} of ~ 0.75 hours post-dose. T_{max} is prolonged in fed state from a median value 0.75 h to 2.5 h. However, these effects were not considered to be of sufficient magnitude to recommend administration instructions based on these findings. Therefore, administration of naldemedine without regard to food intake is acceptable.

Fecal excretion was the major route of elimination (64.3 % of total radioactivity), and mean recovery was ~ 20 % in urine.

Drug-Drug Interactions (DDI)

In *in vitro* studies, naldemedine and its major metabolite did not inhibit or induce major CYP450 enzymes. In addition, the drug and metabolite did not inhibit major transporters.

Because naldemedine is a CYP3A4 substrate to nor-naldemedine and it is also a sensitive p-gp substrate, *in vivo* drug-drug interaction studies were conducted to evaluate the effect of moderate and strong CYP3A4 inhibitors (fluconazole and itraconazole), a strong CYP3A4 inducer (rifampin), and a p-gp inhibitor (cyclosporine) on the PK of naldemedine and its major metabolite. PBPK modeling approach was used to evaluate untested DDI scenarios on naldemedine PK.

Table 3 shows the DDI study results, the Applicant's proposed naldemedine dosing based on DDI studies, and the Clinical Pharmacology Review Team's dosing recommendations.

In the presence of the strong CYP3A4 inducer rifampin, a marked decrease in the C_{max} and AUC of naldemedine were observed. Therefore, the Clinical Pharmacology reviewer agreed with the proposed recommendation to avoid dosing of naldemedine with strong CYP3A4 inducers due to the likelihood of decreased efficacy.

The Applicant also proposed [REDACTED] (b) (4)

[REDACTED] However, only ~1-fold and ~3-fold increases in C_{max} and AUC, respectively, were observed, with co-administration of itraconazole. In addition, adverse event and study discontinuation rates in subjects receiving CYP3A and/or p-gp inhibitors inhibitor did not differ markedly from those not receiving these medications (see Tables 4-7). From an exposure-response perspective, patients with concomitant CYP3A4 inhibitors in the phase 3 Trials 231 and 232 did not appear to exhibit a higher adverse event rate for GI disorders, including abdominal pain, nausea/vomiting, and diarrhea AEs. Together, the Clinical Pharmacology

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Review team did not consider naldemedine dosage adjustment or avoidance of treatment in patients receiving CYP3A4 inhibitors (either moderate or severe) or p-gp inhibitors to be warranted.

Table 3: Summary of Naldemedine DDI Study Findings and Related Dosing Recommendations

Interacting Drug, DDI Category, Fold changes	Applicant's Dosing Proposals	Clin Pharm Recommendations	Rationale
Rifampin; Strong CYP3A4 inducers; C _{max} : 0.62-fold AUC: 0.17-fold	Avoid dosing with strong CYP3A4 inducers	Acceptable	Marked decrease in C _{max} and AUC with rifampin will likely result in loss of efficacy; A potential for increased GI (local) adverse events rules out a possibility of increasing dose with CYP inducers
Itraconazole; Strong CYP3A4 Inhibitor; C _{max} : ↑ 1.12-fold AUC: ↑ 2.91-fold	(b) (4)	OCP recommends the general dose of 0.2 mg qd; Add: 'monitor for AEs'	C _{max} was not much altered with strong inhibitors. The relative AUC increase with strong inhibitors is not markedly greater than with moderate inhibitors (2.9 fold vs. 1.9-fold) where a recommendation of 'no dose adjustment' with AE monitoring is found acceptable. (see below) E-R analysis suggests a greater role for local (gut) concentrations/dose rather than systemic exposures in AEs Population PK analysis shows that drug exposures [median (Range)] in patients cover the nearly 3-fold exposure noted with strong inhibitors;
Fluconazole; Moderate CYP3A4 Inhibitor; C _{max} : ↑ 1.38-fold AUC: ↑ 1.89-fold	No dose adjustment	Acceptable; Add: 'monitor for AEs'	Experience in phase 2b trial with doses up to 0.4 mg qd; E-R analysis suggests local contribution to adverse events rather than systemic exposure; Some trend for higher GI AEs but not markedly higher that would warrant dose adjustment in the overall phase 3 patients who were on concomitant moderate CYP3A or p-gp inhibitors; no difference in abdominal pain and diarrhea vs. those who did not receive the drug. No increased incidence of study discontinuation in phase 3 patients on these inhibitors; No evidence (data) that a lower dose or a less frequent dosing regimen will be efficacious; a lower dose strength is unavailable
Cyclosporine; P-gp Inhibitor; C _{max} : ↑ 1.44-fold AUC: ↑ 1.78-fold	No dose adjustment	Acceptable; Add: 'monitor for AEs'	See rationale under moderate CYP3A inhibitors

(Source: Table 13 from the Clinical Pharmacology Review by Dr. Sandhya Apparaju, page 28)

AE, adverse event; AUC, area under the curve; C_{max}, maximum concentration, Clin Pharm, clinical pharmacology; GI, gastrointestinal; P-gp, P-glycoprotein

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Table 4: Gastrointestinal (GI) Adverse Event Rates in Pooled, Placebo-Controlled Phase 3 Clinical Trials, Stratified by Concomitant P-gp or CYP3A4 Inhibitor Use

	PGP Inhibitor		CYP Inhibitor		
	No	Yes	No	Yes, Moderate	Yes, Strong
% with GI Disorder	23.7%	24.4%	23.3%	22.2%	80.0%
N with GI Disorder	114	10	114	6	4
% with Ab Pain	9.8%	4.9%	9.4%	3.7%	40.0%
N with Ab Pain	47	2	46	1	2
% with Diarrhoea	8.3%	2.4%	8.0%	3.7%	20.0%
N with Diarrhoea	40	1	39	1	1
% with Vomiting	6.4%	4.9%	6.1%	7.4%	20.0%
N with Vomiting	31	2	30	2	1
Total N	481	41	490	27	5

(Source: Table 18, Clinical Pharmacology review by Sandhya Apparaju, page 33/84)

Table 5: GI Adverse Event Frequency in the Phase 3 Program by CYP3A and P-gp inhibitor use and Trial

	V9231		V9232		V9235		Overall	
	NAL		NAL		NAL		NAL	
	0.2 mg N=271	PBO N=272	0.2 mg N=271	PBO N=274	0.2 mg N=621	PBO N=619	0.2 mg N=1163	PBO N=1165
P-gp inhibitor	20.0% (3/15)	23.5% (4/17)	26.9% (7/26)	20.0% (5/25)	29.9% (20/67)	15.9% (10/63)	27.8% (30/108)	18.1% (19/105)
Moderate CYP3A inhibitor	25.0% (3/12)	22.2% (4/18)	20.0% (3/15)	9.1% (1/11)	39.5% (15/38)	7.9% (3/38)	32.3% (21/65)	11.9% (8/67)
Strong CYP3A inhibitor	0.0% (0/2)	50.0% (1/2)	100.0% (4/4)	25.0% (1/4)	100.0% (1/1)	0.0% (0/5)	71.4% (5/7)	18.2% (2/11)
None of inhibitor	19.3% (48/249)	10.1% (25/247)	18.9% (45/238)	13.8% (34/246)	21.5% (116/540)	15.1% (82/543)	20.4% (209/1027)	13.6% (141/1036)

NAL: Naldemedine, PBO: Placebo

(Source: Table 23, Clinical Pharmacology review by Sandhya Apparaju, page 39/84)

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Table 6: Abdominal Pain Incidence in the Phase 3 Program by CYP3A and P-gp inhibitor use and Trial

	V9231		V9232		V9235		Overall	
	NAL	PBO	NAL	PBO	NAL	PBO	NAL	PBO
	0.2 mg N=271	N=272	0.2 mg N=271	N=274	0.2 mg N=621	N=619	0.2 mg N=1163	N=1165
F-gp inhibitor	6.7% (1/15)	0.0% (0/17)	3.8% (1/26)	0.0% (0/25)	10.4% (7/67)	3.2% (2/63)	8.3% (9/108)	1.9% (2/105)
Moderate CYP3A inhibitor	8.3% (1/12)	0.0% (0/18)	0.0% (0/15)	0.0% (0/11)	15.8% (6/38)	2.6% (1/38)	10.8% (7/65)	1.5% (1/67)
Strong CYP3A inhibitor	0.0% (0/2)	0.0% (0/2)	50.0% (2/4)	0.0% (0/4)	0.0% (0/1)	0.0% (0/5)	28.6% (2/7)	0.0% (0/11)
None of inhibitor	8.4% (21/249)	2.8% (7/247)	7.1% (17/238)	1.6% (4/246)	10.2% (55/540)	4.8% (26/543)	9.1% (93/1027)	3.6% (37/1036)

NAL: Naldemedine, PBO: Placebo

(Source: Table 24, Clinical Pharmacology review by Sandhya Apparaju, page 39/84)

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Table 7: Study discontinuations in the Phase 3 Program by CYP3A and P-gp inhibitor use and Trial

	V9231		V9232		V9235	
	Naldemedine 0.2 mg N=271	Placebo N=272	Naldemedine 0.2 mg N=271	Placebo N=274	Naldemedine 0.2 mg N=621	Placebo N=619
	Withdrawals	38/271 (14.0%)	34/272 (12.5%)	34/271 (12.5%)	43/274 (15.7%)	208/621 (33.5%)
CYP3A inhibitor MODERATE	0/12 (0.0%)	2/18 (11.1%)	1/15 (6.7%)	3/11 (27.3%)	23/71 (32.4%)	12/55 (21.8%)
STRONG	1/2 (50.0%)	0/2 (0.0%)	2/4 (50.0%)	1/4 (25.0%)	2/10 (20.0%)	2/10 (20.0%)
NONE	37/257 (14.4%)	32/253 (12.6%)	31/252 (12.3%)	39/259 (15.1%)	184/544 (33.8%)	192/555 (34.6%)
P-gp inhibitor INHIBITOR	1/15 (6.7%)	3/17 (17.6%)	2/27 (7.4%)	6/25 (24.0%)	22/89 (24.7%)	15/84 (17.9%)
NONE	37/256 (14.5%)	31/255 (12.2%)	32/244 (13.1%)	37/249 (14.9%)	186/532 (35.0%)	191/535 (35.7%)

(Source: Table 25, Clinical Pharmacology review by Sandhya Apparaju, page 39)

Exposure-Response

Exposure-response data for the PK/PD analysis population from Studies V9231 and V9232 (Naldemedine 0.2 mg: n=445, placebo: n=548) are shown in Table 8. In this table, proportions of SBM responders (primary efficacy endpoint; see Section 7.1.1 for endpoint definition) are presented by AUC group [placebo (0 ng·hr/mL) and 7 AUC ranges—0 to <10, 10 to <15, 15 to <20, 20 to <25, 25 to <30, 30 to <35, ≥35 ng·hr/mL].

With the exception of the lowest AUC group (<10 ng·hr/mL), the proportions of SBM responders were >50% and similar to the SBM responder rates in the naldemedine arm of the primary analysis population (ITT) for Studies V9231 and V9232 (47.6% and 52.5%, respectively).

In the lowest naldemedine AUC group (<10 ng·hr/mL), the proportion of SBM responders was 16.7%, which was also lower than responder rate in the placebo group (34.1%). However, this group only consisted of 24 subjects (5.4% of the naldemedine patients).

For the 10 to <15 ng·hr/mL AUC group, in which patients showed ~ 50% lower systemic exposure compared with the mean AUC of 27.50 ng·hr/mL, the proportion of SBM responders

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(61.3%) was also within the 50-60% proportion of SBM responders, as observed in the groups of subjects with AUC >15 ng·hr/mL.

Table 8: Proportion of SBM responders by systemic exposure (AUC) in Studies V9231 and V9232

AUC (ng·hr/mL)	Number of Subjects	Number of SBM Responders	Number of SBM Non-responders	Proportion of SBM Responders
0 (Placebo)	548	187	361	34.1%
>0 to < 10	12	2	10	16.7%
10 to < 15	31	19	12	61.3%
15 to < 20	65	36	29	55.4%
20 to < 25	128	71	57	55.5%
25 to < 30	78	41	37	52.6%
30 to < 35	38	20	18	52.6%
> 35	93	48	45	51.6%

[Source: Table 1, "Proportion of SBM responders by systemic exposure (AUC) in Studies 1314V9231 and 1315V9232", Response to FDA Clinical Information Request, page 2/4; Module 1.11.3, NDA 208854]

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable

4.8. Foreign Regulatory Actions and Marketing History

At the time of this report, naldemedine has not been approved for marketing in any country. To date, a marketing application has also been submitted in Japan.



5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 9: Summary of Naldemedine Clinical Trials

Phase	Study Population	Design	Duration	Location	n (trials)
3	OIC & chronic non-cancer pain	Double-blind	12 weeks	Global	2
		Double-blind safety	52 weeks	Global	1
		Open-label safety	48 weeks	Japan	1
	OIC on treatment with oxycodone hydrochloride for chronic non-cancer pain	Open-label safety	48 weeks	Japan	1
	OIC & chronic cancer pain	Double-blind	14 days	Japan	1
		Open-label extension	12 weeks	Japan	1
2a	Chronic opioid use	Single ascending dose	1 day	Global	1
2b	OIC & chronic non-cancer pain	Double-blind	28 days	Global	1
	OIC & Chronic cancer pain	Double-blind	14 days	Japan	1
1	Healthy individuals	Variable (PK, metabolism, and clinical safety studies)	Variable	Variable	12

(Source: Reviewer's Table)

Abbreviations used in table: n, number; OIC, opioid induced constipation; PK, pharmacokinetic

The primary sources of clinical data for this NDA are three phase 3 clinical trials conducted in patients with OIC and chronic non-cancer pain—Studies 1314V9231, 1315V9232, and 1326V9235. Hereafter, these clinical trials will be referred to by their abbreviated names (V9231, V9232, and V9235, respectively), in the manner used by the Applicant in Clinical Study Reports and Clinical Summaries.

Studies V9231, V9232, and V9235 are all multicenter, randomized, double-blind, parallel group trials. Studies V9231 and V9232 are replicate 12-week trials conducted to evaluate the safety and efficacy of naldemedine in adults with OIC and chronic non-cancer pain. Study V9235 is an ongoing, 52-week trial with the primary objective to assess the long-term safety of naldemedine in this patient population.

A tabular listing of the other 19 naldemedine clinical trials is located in Appendix 13.4.

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5.2. Review Strategy

The efficacy evaluation of naldemedine for treatment of OIC in patients with chronic non-cancer pain was based primarily on clinical trial data from Studies V9231 and V9232, two replicate phase 3 efficacy studies. Supportive efficacy data were also submitted from the long-term safety trial (Study V9235).

Studies V9231 and V9232

For the clinical review, the body of evidence used to determine the effectiveness of naldemedine for the treatment of OIC in adults with chronic, non-cancer pain included data for the protocol-defined primary endpoint and 4 key secondary endpoints.

The primary endpoint for these 2 trials was based on a pre-specified responder definition that was consistent with the primary endpoint used in other clinical development programs for OIC and similar treatment indications and is considered to represent a clinically meaningful treatment effect.

For each of the 4 key secondary endpoints, the analysis consisted of a comparison of group means for the change from baseline in frequency of a pre-defined bowel movement (BM) event at a specified timepoint, which, unlike the primary endpoint, lacks inherent clinical meaningfulness. Based on recommendations provided by Clinical Outcomes Assessment (COA) team, the Division requested that the Applicant conduct correlations of secondary endpoint data with subject global satisfaction (SGS) scores, in an effort to link these data with a measure of how patients feel or function. For each of the 3 endpoints which compared BM event frequency at baseline and the last 2 weeks of the treatment period, cumulative distribution function (CDF) plots of change in BM event frequency were developed, one set with curves for SGS score (pooled treatment arms) and one set with curves for treatment groups. Unfortunately, closer evaluation of the SGS assessment itself revealed that the wording of the SGS query was not adequate to ensure that patient's satisfaction rating was specific to their perceived change in constipation-related symptoms. The COA team concluded that interpretability of these correlations as an indication of the clinical meaningfulness of secondary outcome assessments may have been compromised.

For this application, consideration was also given to prior results from clinical trials of other PAMORAs in order to provide a context in which to assess the clinical meaningfulness of the responder rates and treatment effect size observed in these trials.

Study V9235

Unlike Studies V9231 and V9232, Study V9235 did not have a pre-specified primary efficacy endpoint. The Applicant collected efficacy data throughout the trial. However, because specified time points for efficacy endpoints were not pre-specified and variability in

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concomitant laxative use was permitted without adequate methods to control for treatment differences, efficacy data from this trial were not pivotal to the overall determination of effectiveness.

6 Review of Relevant Individual Trials Used to Support Efficacy

Study V9231

6.1.1. Study Design

Overview and Objective

Title: A Randomized, Double-blind, Placebo-controlled, Parallel-group Study of Naldemedine in the Treatment of Opioid-induced Constipation (OIC) in Subjects with Non-malignant Chronic Pain Receiving Opioid Therapy

Study Objectives: To evaluate the efficacy and safety of naldemedine compared to placebo for the treatment of OIC in adults receiving chronic opioid treatment for chronic, non-cancer pain.

Study V9231 was conducted from 29 August 2013 (date of enrollment of first patient) through 22 January 2015 (completion of the last subject).

Trial Design

Study V9321 was a phase 3, randomized, double-blind, parallel-group clinical trial comparing treatment with naldemedine 0.2 mg once daily with placebo. (Note that Study V9232 had the same clinical trial design as Study V9231.)

The total length of trial participation was 18-20 weeks, divided into 3 periods:

- Screening Period: 2- to 4-weeks, including a 14-consecutive-day qualifying period
- Treatment Period: 12-week double-blind, placebo-controlled period of study treatment
- Follow-up Period: 4-week observation period without study treatment

This reviewer considers the randomized, double-blind, parallel-group trial design of Study V9231 (and V9232) to represent an adequate and well-controlled clinical trial design to serve as the basis of the efficacy evaluation for naldemedine for the proposed indication.

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Study Population

The planned study population was approximately 540 subjects, randomized in a 1:1 ratio to one of 2 treatment arms (270 subjects each) —naldemedine 0.2 mg or placebo once daily.

Study Eligibility Assessments and Criteria to Define OIC and Minimum Opioid Usage

To determine study eligibility, an evaluation of subjects' baseline constipation status (i.e., BM frequency and consistency, need for rescue medication, presence of specified constipation-related symptoms) and intake of opioid medications [i.e., average today daily dosage (TDD)] was performed over a 14-consecutive-day qualifying period as part of the study Screening Period and prior to study treatment randomization. These baseline evaluations were based on subjects' daily self-reports of OIC-related data, submitted using an eDiary format, using the same procedures as efficacy data collection during the subsequent Treatment Period.

Prior to initiation of the trial, subjects were required to discontinue all laxative use (e.g., stool softener, bulking agents, GI tract stimulants, prokinetic agents, suppositories, enemas, or other medications/agents used to treat constipation). Subjects were provided with bisacodyl tablets, which were the only laxatives permitted during study participation for use as rescue treatment. Rescue treatment was permitted after a period of 72 hours without BM, as instructed in the Rescue Laxative Guidelines of the Study Protocol.

To be eligible for participation in Study V9231, subjects were required to meet pre-specified criteria for OIC diagnosis and opioid usage. This reviewer considers the pre-specified criteria appropriate and adequately defined to ensure enrollment of (1) subjects with an accurate diagnosis of OIC, (2) a study population that adequately reflects the intended treatment population, and (3) subjects with baseline disease severity sufficient for evaluation of treatment effect.

OIC-Related Eligibility Criteria

(A subject had to meet all criteria to be eligible for participation in Study V0231)

OIC-Related Eligibility Criteria

(A subject had to meet all criteria to be eligible for participation in Study V0231)

- Diagnosis of OIC (by self-report), defined as:
 1. Frequency of SBM of:
 - 1) ≤ 4 spontaneous bowel movements (SBM), total over the 14 days
AND
 - 2) ≤ 3 SBMs in a given week of the qualifying period
AND
 2. Presence of ≥ 1 of the following bowel symptoms in $\geq 25\%$ of BMs:

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- 1) Presence of straining
 - 2) Lumpy or hard stools
 - 3) Sensation of incomplete evacuation
 - 4) Sensation of anorectal obstruction/blockage
- Documented medical history of chronic non-cancer pain for which the subject has received treatment with opioid medication for ≥ 3 months duration
 - Stable opioid regimen for ≥ 1 month prior to screening
 - Average total daily dose (TDD) of opioid medication ≥ 30 mg equivalents of oral morphine sulfate

Because the primary data source of efficacy data for Study V9231 was the subject eDiary, subject compliance with eDiary procedures was crucial to ensure collection of adequate data for efficacy analyses. Therefore, evaluation of study eligibility during the 14-consecutive-day qualifying period also included an assessment of subjects' ability to understand and comply with eDiary procedures, which included a minimum required compliance rate of 78% (i.e., completion of ≥ 11 of 14 daily eDiary entries during the qualifying period).

Study Definitions

Bowel Movement Events

- Spontaneous Bowel Movement (SBM): a BM that occurs without the use of a rescue laxative medication during the 24 hours prior to the BM.
Note that any number of SBMs with a Bristol Stool Scale rating of "1" within a 2-hour period was counted as a single SBM.
- Complete Spontaneous Bowel Movement (CSBM): a BM without rescue laxative use in the prior 24 hours that is accompanied by feeling of complete evacuation.
Assessments of CSBM frequency were performed in the same manner as SBM assessments.
- Frequency of SBMs per week: A calculation of SBM frequency based on the number of SBMs reported, corrected for the number of eDiary entries for the week, using the following formula:

$$\text{Frequency of SBMs per week} = \frac{\text{Total number of SBMs in the week} \times 7}{\text{\# days of observation related to defecation in the week}}$$

[The "number of days of observation related to defecation" was defined as the number of eDiary entries containing the requisite efficacy data related to defecation for the week. A minimum of 4 eDiary entries related to defecation was required for a treatment week to be evaluable.]

The definitions for SBM and CSBM used for efficacy assessments in Study V9231 are consistent with terminology used across clinical trials for OIC and other constipation disorders. However, the definition of "frequency of SBMs per week" used for baseline and efficacy assessments was

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a derived value which adjusted the observed number of SBM in a week based on the number of completed eDiary entries. The rationale for derivation of adjusted values for efficacy assessments, rather than using the actual number of observed (i.e., subject-reported) SBMs, was to account for the relatively high rate of missing and/or incomplete eDiary data, which the Applicant attributed to challenges related to daily eDiary requirements.

However, the appropriateness of adjustment of SBM frequencies relies on an assumption that SBMs were equally likely occur on days for which a subject did not complete an eDiary entry as days with a completed entry. However, this reviewer is concerned that completion of eDiary entries may be subject to response bias, whereby subjects are more likely to complete eDiary entries in the case of events, such as SBMs or use of rescue medication, and less likely to complete entries on days without such events. Consequently, adjustment of SBM frequency based on the number of eDiary entries could have resulted in the overestimation of naldemedine treatment effect and magnified the difference in responder proportions between the naldemedine and placebo treatment arms. However, the degree to which efficacy results could be skewed by using the derived values for SBM frequency per week was limited by the requirement of ≥ 4 eDiary entries for a week.

The various components of the responder definition used for efficacy analyses and the impact of missing and non-evaluable data on efficacy results are discussed further with respect to pre-specified study endpoints and statistical analyses.

Eligibility Criteria

The following is a summary of all key study eligibility criteria:

➤ Key Inclusion Criteria:

1. Age 18 to 80 years of age, inclusive, at the time of informed consent
2. Meets criteria for a diagnosis of OIC* and has documented chronic non-cancer pain for which the subject has been receiving opioid treatment for ≥ 3 months (see above*)
3. Stable opioid regimen at a TDD on average of ≥ 30 mg equivalents of oral morphine sulfate for ≥ 1 month prior to Screening (see above*)
4. Not taking laxatives at the time of screening or is willing to discontinue laxative use (e.g., stool softener, bulking agents, GI tract stimulants, prokinetic agents, suppositories, enemas, or other medications/agents used to treat constipation); and willing to use only the rescue laxatives provided during the Screening and Treatment Periods
5. Met assessment criteria from the 14-consecutive-day qualifying period, related to (1) BM frequency, (2) presence of related bowel symptoms, and (3) eDiary compliance, as defined above
6. Meets the following reproductive-related criteria:

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- For males: either sterile for 6 months prior to Screening (e.g., vasectomy) or agreed to use an approved method of contraception (use of a condom with spermicide from the start of the Screening Visit until 28 days after the last dose of study drug)
- For females: non-pregnant, non-lactating, and either postmenopausal (defined as cessation of regular menstrual periods for ≥ 1 year if ≥ 50 years old or 2 years if < 50 years old with FSH confirmation), surgically sterile by hysterectomy, bilateral oophorectomy, or agreed to use a highly effective (with failure rates $< 1\%$ per year) technique of birth control from the Screening Visit until 28 days after the last dose of study drug; females of child-bearing potential must have had a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at Visit 2 (Day 1) prior to dosing
- For both sexes: subjects who were not sexually active (abstinent) must have agreed to use one of the above-mentioned methods if they became sexually active while participating in the study

➤ Key Exclusion Criteria:

1. Significant structural abnormalities of the GI tract:
 - a. History of bowel obstructions, stricture
 - b. History of bowel surgery such as bowel resection or bariatric surgeries
2. Active medical diseases affecting bowel transit such as ileus, uncontrolled hypothyroidism, irritable bowel syndrome, inflammatory bowel disease (ulcerative colitis, Crohn's disease, diverticulitis), fecal incontinence
3. History or presence of pelvic disorders that may have been a cause of constipation
4. Surgery (except for minor procedures) within 60 days of Screening, or planned surgery during study treatment that would have influenced pain or bowel function or precluded completion of the study
5. History of chronic constipation prior to starting analgesic medication or any potential non-opioid cause of bowel dysfunction that may have been a major contributor to the constipation (e.g., mechanical GI obstruction)
6. Severe constipation that had not been appropriately managed such that the subject was at immediate risk of developing serious complications of constipation. This included subjects who had reported no BMs for 7 consecutive days prior to and during the Screening Period
7. Subjects who had never taken laxatives for the treatment of OIC
8. Initiation of a new bowel regimen or prokinetic agent, or significant change in diet supplement use, or exercise regimens within 28 days of the Screening Visit

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9. History of active treatment for cancer within the last 2 years of Screening (except for basal cell or squamous cell carcinoma of the skin that had been successfully resected, or tamoxifen and raloxifene when being used for prevention of breast cancer)
10. Abnormal screening laboratory test result(s), including:
 - a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times the upper limit of normal (ULN)
 - b. Total bilirubin >1.5 times the ULN
 - c. Serum creatinine >1.5 times the ULN
11. Significant comorbid medical condition(s), including but not limited to cardiovascular (CV), respiratory, hepatic, renal, or endocrine dysfunction, or human immunodeficiency infection, to the extent that study participation is not considered to be subject's best interest or may interfere with study compliance/completion.
12. Significant CV risk such as presence or suspected presence of unstable coronary artery disease, myocardial infarction, stroke, or transient ischemic attack within 3 months of Screening
13. Any medical or psychiatric condition that, in the opinion of the Investigator, may have compromised the ability of the subject to understand and comply with the study protocol or provide informed consent to participate in the study
14. Positive results for serologic tests for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), or active hepatitis A virus (HAV)
15. Use at Screening of any prohibited medication, including opioid antagonists, partial agonists, or mixed agonist/antagonists
16. History of illegal drug use in the last 2 years of Screening, documented misuse of prescribed medications or a positive urine drug screen, with the exception of findings consistent with administration of prescribed medications
17. Allergic reaction to opioids or known or suspected hypersensitivity to naltrexone hydrochloride, methylnaltrexone bromide, naloxone hydrochloride, alvimopan, or any other opioid antagonist
18. Treatment with an investigational product within 2 months prior to the Screening Visit
19. Prior participation in naldemedine trials

Study eligibility for Study V9231 was generally consistent with the eligibility for participation in clinical trials for similar products, and the pre-specified inclusion/exclusion criteria sufficient reflect the target treatment population for the proposed indication. Similarly, the pre-specified OIC-related definitions and methods for quantifying opioid use were appropriate to ensure enrollment of patients with OIC support the proposed indication.

This reviewer notes, however, that protocol amendments were issued to clarify inclusion criteria and disease-related definitions. Although these protocol changes were instituted after

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enrollment had already been initiated, no notable impact on the clinical trial population or efficacy results was noted during this review.

Study Treatment

The study drug (naldemedine 0.2 mg or placebo) used for the Treatment Period was supplied in bottles of 36 tablets in double-blinded manner, labeled with the subject's randomization number, number of tablets, cautionary statement, and storage conditions. Clinical trial sites dispensed the medication directly to study subjects during Study Visits.

The naldemedine formulation consisted of an oral tablet, containing 0.2 mg of the active compound. Placebo tablets were identical to active tablets in appearance, taste, color, and odor. Subjects were instructed to take one tablet of the dispensed study drug by mouth once daily, regardless of randomization assignment. Naldemedine was administered without regard to food. Administration instructions also specified that subjects should identify the most appropriate time for dosing each day that would maximize compliance with dosing and convenience relative to the occurrence of BMs, and every effort should be made to take the study drug at approximately the same time each day throughout the Treatment Period. Subjects were required to capture the time of administration of the study drug by eDiary for only the first 14 days of dosing.

Dose Selection:

A single naldemedine dosage regimen (0.2 mg once daily, administered as an oral fixed-dose tablet) has been used in all phase 3 clinical trials. No dose modifications have been made during the planning or conduct of naldemedine phase 3 clinical trials.

The rationale for the dose selection of naldemedine for the phase 3 clinical trials to support this NDA was mainly based on the phase 2 clinical trial which evaluated 2 naldemedine doses (0.1 mg and 0.2 mg) vs. placebo.

Assignment to Study Treatment:

- Randomization Procedures: Subjects were to be randomized within a maximum of 7 days of meeting the eligibility requirements. At randomization, subjects were stratified based on their documented opioid use (average TDD during the 14-consecutive-day qualifying period of either 30 to 100 mg equivalents of oral morphine sulfate or >100 mg equivalents of oral morphine sulfate. Randomization utilized a centralized interactive voice recognition system (IVRS)/Interactive Web Response System (IWRS).
- Blinding Procedures: Subjects, the Investigator, all study personnel, and data analysts were blinded to the treatment assignment until database lock. Treatment assignments for study drug administration were concealed by the use of identical packaging, labeling, dosing instructions, appearance, taste, color, and odor. The randomization schedule was kept

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confidential and was only accessible to the Drug Supply Management staff, IVRS/IWRS Clinical Coordinator(s), IVRS/IWRS vendor staff, unblinded statistician on the Data Safety Monitoring Board, and in cases of Suspected Unexpected Serious Adverse Reactions, as required by local regulation, until database unlock.

Treatment Compliance:

Assessments of treatment compliance by the Investigator and/or site personnel were performed during each study visit, including:

- Tablet counts performed by qualified site personnel to verify that the correct number of doses were taken based on the actual number of days that had elapsed between clinic visits
- Information provided to the Investigator/staff by the subject during Study Visits
- eDiary records (only collected for the first 14 days of the Treatment Period)

If noncompliance with study medication was identified, site personnel were supposed to counsel subjects, and if non-compliance persisted (dosing compliance <80%), the subject was to be withdrawn from the study. In the event that a subject was withdrawn for compliance reasons, the Investigator was responsible for notification of the Application or designee and to make every effort to complete the Early Termination assessments and the Early Termination/Study Completion eCRF. All subject discontinuations were supposed to be registered in the IVRS/IWRS system.

Prior and Concomitant Medications/Therapies

All medications (prescription and over-the-counter) taken by the subject for 3 months prior to Screening, and concomitant medications taken with the study drug through the end of the study were recorded in the CRF.

Concomitant Opioid Therapy

By definition of the study population, all subjects enrolled in this study were receiving opioid therapy for chronic, non-cancer pain. To be eligible for study participation, a subject was required to have been treated with opioids for ≥ 3 months, with a stable opioid regimen at a TDD on average of ≥ 30 mg equivalents of oral morphine sulfate for ≥ 1 month prior to Screening and without anticipated changes in their overall opioid regimen during study participation. Opioid therapy was not provided as part of the study, as subjects were required to be on a stable opioid regimen prior to the Screening Visit.

Subjects were permitted to take additional medication (opioid or non-opioid) for breakthrough pain as prescribed by their physician. At the screening visit, all opioid medication(s) taken by the subject during the prior 3 months were recorded on the eCRF. All pain medication(s) (opioid or non-opioid) were recorded by the subject throughout the study.

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Use of tramadol and tapentadol were permitted in this study. Tramadol and tapentadol have a dual mechanism of action, including opioid-mediated analgesia. However, these medications are considered weak opioids and are associated with less constipation than other opioids. Therefore, to ensure that subjects were receiving an adequate opioid dose, tramadol and tapentadol were not included in the calculations for either the stable opioid regimen at a TDD on average of ≥ 30 mg equivalents of oral morphine sulfate for eligibility assessment, or stratification by average TDD.

Laxative Therapy

Prior to initiation of study participation, subjects must have agreed to discontinue all laxative use (e.g., stool softener, bulking agents, GI tract stimulants, prokinetic agents, suppositories, enemas, or other medications/agents used to treat constipation) from the start of Screening through the end of the Treatment Period. Every attempt was made to limit laxative use during the 24-hour period immediately prior to randomization.

During the Screening and Treatment Periods, subjects were provided bisacodyl tablets by the Applicant for use as rescue laxative therapy. Rescue treatment was permitted if subjects did not have a BM over a period of 72 hours, as outlined in the Rescue Laxative Guideline in the Study Protocol. Use of other laxatives/medications for treatment of constipation was prohibited and could have resulted in premature discontinuation from study participation.

All rescue laxative therapy during the Screening and Treatment Periods was to be documented in the eDiary, including the laxative name, dose taken, and the date and time of administration. Study drug treatment was continued during rescue laxative treatment.

Prohibited Concomitant Medications

Use of the following medications was prohibited at any time during study participation and could result in study discontinuation:

- Opioid antagonists (alvimopan, methylnaltrexone bromide)
- Acetylcholine agonists (bethanechol)
- Guanylate cyclase-C agonist (linaclotide)
- 5-HT-4 agonists (prucalopride)
- Prostaglandin (misoprostol)
- Mu receptor partial agonist opioids (meptazinol)
- Mixed agonist/antagonist (nalorphine-like agonist/antagonist opioids; e.g., pentazocine, buprenorphine) Antispasmodics (dicyclomine)
- Antidiarrheals (loperamide)
- Prokinetics (metoclopramide)
- Chloride channel activator (lubiprostone)

Any additional medications that could have had a significant impact on the GI system or bowel habits may have been prohibited at the Investigator's discretion.

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Version date: June 25, 2015 for initial rollout (NME/original BLA reviews)

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Other (Non-medication) Study Restrictions/Dietary Restrictions

- Subjects were not to initiate any new diets, supplement changes, or exercise regimes during Screening and throughout the study.
- Manual removal of stool (i.e., manual disimpaction) was not allowed and disqualified a subject from further participation in the study.

Study Endpoints

Primary Endpoint

The primary efficacy endpoint was the proportion of “responders”, in which a “responder” was defined as a subject who achieved both:

- ≥ 9 “positive-response weeks” out of the 12-week Treatment Period and
- ≥ 3 “positive-response weeks” out of the last 4 weeks of the 12-week Treatment Period

In which a “positive-response week” was defined as:

- ≥ 3 SBMs per week and
- An increase from baseline of ≥ 1 SBM per week for that week

As previously mentioned, a minimum of 4 days of eDiary entries related to defecation was required for a treatment week to be considered evaluable. If < 4 days of eDiary entries related to defecation were available for a treatment week, that week was considered non-evaluable and was treated as a “non-response” week.

Also, the frequency of SBMs per week was derived using the following formula which adjusts the number of reported SBMs per week for the number of eDiary entries completed:

$$\text{Frequency of SBMs per week} = \frac{\text{Total number of SBMs in the week} \times 7}{\text{\# days of observation related to defecation in the week}}$$

These data handling procedures apply to all study endpoints using the variable “Frequency of SBM [or CSBM] per week.”

Secondary Endpoints

Four secondary endpoints were pre-specified in the clinical trial protocol:

1. Change in the frequency of SBMs per week from baseline to the last 2 weeks of the Treatment Period (to assess for persistence of effect)
2. Change in the frequency of SBMs per week from baseline to Week 1 of the Treatment Period
3. Change in the frequency of CSBMs per week from baseline to the last 2 weeks of the Treatment Period
4. Change in the frequency of SBMs without straining per week from baseline to the last 2 weeks of the Treatment Period

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Exploratory Endpoints:

The Applicant also performed data analyses for the following exploratory endpoints:

1. Proportion of complete SBM (CSBM) responders (using the same responder definition as SBM for the primary endpoint)
2. Proportion of SBM responders in any 6 weeks of the 12-week Treatment Period
3. Proportion of SBM Responders in any 9 weeks of the 12-week Treatment Period
4. Change in each of the following 8 variables related to defecation per week from baseline to each week of the Treatment Period:
 - 1) Frequency of SBMs with BSS of 3 or 4 per week
 - 2) Frequency of SBMs per week
 - 3) Frequency of CSBMs per week
 - 4) Frequency of SBMs without straining per week
 - 5) Frequency of SBMs without blockage per week
 - 6) Number of days with at least 1 SBM per week
 - 7) Number of days with at least 1 CSBM per week
 - 8) Proportion of Responders by Opioid Dose Strata
5. Time to the first SBM and CSBM after initial dose of study drug
6. Incidences of SBM and CSBM within 4, 8, 12, 24, and 48 hours of initial study drug dose
7. Change in maximal number of days between SBMs from baseline for each 2-week period of the Treatment Period
8. Change in each variable (see exploratory endpoint 4) related to rescue laxative per week from baseline to each week of the Treatment Period
9. Change in the abdominal bloating and abdominal discomfort scores from baseline to each week of the Treatment Period
10. Change from baseline in overall and each domain for PAC-SYM and PAC-QOL Change from baseline in overall SF-36 and each domain of SF-36
11. Subject Global Satisfaction

Study Procedures

Study V9231 included 8 scheduled study visits over the 3 study periods (screening, treatment, and follow-up).

- Screening Period: 1 study visit
 - Visit 1: Day -28 to Day -14 days (minimum 14 days prior to randomization)
- Treatment Period: 6 study visits
 - Visit 2: Day 1
 - Visit 3: Week 1
 - Visit 4: Week 2
 - Visit 5: Week 4
 - Visit 6: Week 8

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- Visit 7: Week 12
- Follow-up Period: 1 study visit
- Visit 8: Week 16

Planned Assessments

Scheduled study assessments by Study Visit for Study V9231 are shown in Table 10. (Note that planned study procedures were the same as Study V9232.)

Table 10: Scheduled Assessments in Studies V9231 and V9232

	Evaluation	Screening Period	Treatment Period						Follow-up Period	Early Termination Visit (≤4 weeks after last dose of study drug)	Unscheduled Visit(s) (at the discretion of the Investigator)
		Visit 1; Up to -28 days Prior to Randomization (Minimum 14 Days)	Visit 2; Day 1	Visit 3; Week 1 (±3 days)	Visit 4; Week 2 (±3 days)	Visit 5; Week 4 (±3 days)	Visit 6; Week 8 (±3 days)	Visit 7; Week 12 (+3 days)	Visit 8; Week 16 (±7 days)		
<i>Study Eligibility</i>	Informed Consent	X									
	Inclusion/Exclusion Criteria	X	X								
<i>Clinical Evaluation</i>	Demographics	X									
	Medical History	X	X								
	Physical Examination	complete	focused	focused	focused	focused	focused	complete	focused	complete	focused
<i>Investigations (Laboratory/Diagnostic Studies)</i>	Vital Signs	X	X	X	X	X	X	X	X	X	X
	12-lead Electrocardiogram	X						X		X	
	Hematology	X	X			X	X	X	X	X	
	Serum Chemistry	X	X			X	X	X	X	X	
	Urinalysis	X	X			X	X	X	X	X	
	Urine Drug Screen	X									
	Pregnancy Test (Serum or Urine)	Serum	Urine					Urine	Urine	Urine	
	Serum Endocrine	X	X					X	X	X	
	HAV, HBsAg, HCV	X									
	<i>Clinical Pharmacology</i>	Pharmacokinetics				X	X	X		X	
<i>Study Medications</i>	Randomization		X								
	Study Drug Dispensation		X			X	X				
	Drug Accountability (study)			X	X	X	X	X		X	
<i>eDiary (Self-reported Efficacy Assessments)</i>	Rescue Laxative Dispensation	X	X	X	X	X	X				
	eDiary Training/Compliance Assessment	X	X	X	X	X	X	X			
<i>Investigator-Reported Study Information</i>	BMCA eDiary Completion	X	X	X	X	X	X	X		X	X
	Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X
	Cardiovascular Assessment		X	X	X	X	X	X	X	X	X
	Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X
<i>Questionnaire Assessment Tools</i>	Subject Global Satisfaction						X		X		
	COWS		X	X	X	X	X	X		X	
	SOWS		X	X	X	X	X	X		X	
	PAC-SYM/PAC-QOL		X		X	X		X		X	
	11-Point NRS		X	X	X	X	X	X		X	
	Short Form 36		X					X		X	
	Early Termination/Study Completion eCRF						X		X		

(Source: Adapted from Applicant's Table 9-2, "Schedule of Events", Clinical Study Report: 1314V9231, pages 47-48/1539, and Clinical Study Report: 1315V9232, pages 49-50/1630; NDA 208854, Module 5.3.5.1)

Abbreviations in Table: BMCA, Bowel Movement and Constipation Assessment; COWS, Clinical Opiate Withdrawal Scale; eCRF, electronic case report form; eDiary, electronic diary; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; NRS, Numeric Rating Scale; PAC-SYM/PAC-QOL, Patient Assessment of Constipation-Symptom Questionnaire/Patient Assessment of Constipation-Quality of Life; SOWS, Subjective Opiate Withdrawal Scale

(Source: Applicant's Table 9-2, "Schedule of Events", Clinical Study Report: 1314V9231, page 47/1539)

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Subject eDiary

A subject eDiary format (patient self-report, not accessible to the Investigator and other study site personnel) was used during both the Screening and Treatment Periods to obtain constipation-related data for baseline assessments and efficacy analyses of primary and secondary endpoints. The primary assessment tool used to elicit efficacy data from patients via an eDiary was the Bowel Movement and Constipation Assessment (BMCA, shown below), which captured information regarding the frequency, timing, and characteristics of BMs (e.g., consistency, size), as well as the presence of associated symptoms (e.g., straining with BMs, abdominal bloating, abdominal discomfort). The eDiary was also used to record opioid medication use, as well as the time of study drug administration for the first 14 days of the Treatment period.

Blinding of Investigators and other site study personnel to subjects' self-reported efficacy data using platforms such as an eDiary is a beneficial strategy to minimize bias. Nevertheless, the Applicant identified challenges encountered with eDiary use. The Applicant blamed the eDiary format for a higher-than-expected quantity of missing efficacy data, which occurred despite formal assessments of eDiary compliance and proficiency during the Screening period and exclusion of subjects with inadequate eDiary completion rates.

The purported high rate of incomplete eDiary entries was cited as the basis for post-hoc changes in the definitions of the mITT and PP analysis population. Although these late protocol changes carry risk of introduction of bias into study data, their impact was limited by the pre-specified use of the ITT population (a population unaffected by use of these modified definitions) as the primary efficacy analysis population, the implementation of changes prior to database unblinding, and the fact that mITT and PP efficacy analyses were only 2 of 6 planned sensitivity analyses of the primary endpoint.

Assessments conducted using the eDiary:

- Daily assessment of bowel movement events and constipation-related symptoms [using the Bowel Movement and Constipation Assessment (BMCA)- see details below under efficacy assessments]
- Laxative Use
- Opioid Use

For Primary and Secondary Endpoint Assessments

➤ **Bowel Movement and Constipation Assessment (BMCA):**

The BMCA was the primary tool used to collect constipation-related data for baseline and efficacy assessments. The BMCA comprised the portion of the eDiary used for daily subject self-reports (eDiary entries) to capture data related to BMs and specific constipation-related symptoms. The following is a list of the components of the BMCA:

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- Date and time of BM
- BM Consistency (Score) using the 7-point Bristol Stool Scale (BSS):
 - 1 = separate hard lumps like nuts
 - 2 = sausage shaped but lumpy
 - 3 = like a sausage but with cracks on its surface
 - 4 = like a sausage or a snake, smooth and soft
 - 5 = soft blobs with clear-cut edges
 - 6 = fluffy pieces with ragged edges/mushy stool
 - 7 = watery, no solid pieces, entirely liquid
- Feeling of complete emptying after the BM: (yes/no)
- Sensation that stool could not be passed (i.e., presence of a blockage) during BM: (yes/no)
- Severity of straining (score) with the BM:
 - 1) = no straining
 - 2) = mild straining
 - 3) = moderate straining
 - 4) = severe straining
 - 5) = very severe straining
- Abdominal bloating severity (score) during the 24-hour period prior to the BM:
 - 0 = absent
 - 1 = mild
 - 2 = moderate
 - 3 = severe
 - 4 = very severe
- Abdominal discomfort score for the past 24 hours:
 - 0 = absent
 - 1 = mild
 - 2 = moderate
 - 3 = severe
 - 6) = very severe

Additional Assessments for Exploratory Endpoints

- Subject Global Satisfaction (SGS)
- Short Form 36 (SF-36): 36-item scale to survey health status and quality of life (QOL) by assessing impact of physical and/or emotional problems on physical activities, social activities, usual role activities, bodily pain, general mental health (psychological distress and well-being), vitality (energy and fatigue), and general health perception
- Patient Assessment of Constipation Symptom (PAC-SYM) and Quality of Life (PAC-QOL) Questionnaire [5-point Likert scale: 0=absence of symptom, 1=mild, 2=moderate, 3=severe, and 4=very severe]

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- PAC-SYM: 3 domains (abdominal, rectal, and stool symptoms)
- PAC-QOL: 4 domains (physical discomfort, psychological discomfort, worries and concerns, and dissatisfaction)

The schedule of safety assessments is included in Table 10, and assessments are discussed in Section 8.

Note, that of the additional assessments for exploratory endpoints, only SGS data are discussed.

Study drug discontinuation

Study drug treatment could be discontinued for any of the following reasons:

- Withdrawal from study participation by subject
- Serious or intolerable adverse event(s) considered to be related to study drug or that the Investigator determined that the subject should have been withdrawn because of safety reasons
- Abnormal liver chemistry tests which meet pre-specified discontinuation criteria
- Lost to follow-up
- Pregnancy
- Protocol deviation that resulted in a significant risk to the subject's safety
- Unblinding

In the event of a subject's withdrawal, the Investigator was responsible for notifying the Applicant through the Interactive Voice/Web Response System (IVRS/IWRS) and to make every effort to complete the end-of-study (or Early Termination) assessments. All subjects who withdrew or discontinued were to be followed until resolution of any adverse events or until the unresolved adverse events were judged by the Investigator to have stabilized.

For subjects who were lost to follow-up (i.e., those subjects whose status was unclear because they failed to appear for study visits without stating an intention to withdraw), the Investigator was to record in the source documents all steps taken to contact the subject, (eg, dates of telephone calls, registered letters, etc.). An Early Termination/Study Completion eCRF was to be completed for all subjects who discontinued prematurely or were lost to follow-up.

Statistical Analysis Plan

Efficacy Analysis Populations:

- Intent-to-Treat (ITT) Population: all randomized subjects.
- Modified ITT (mITT) Population: all randomized subjects who received at least 1 dose of study drug and completed the first 4 weeks of the study with at least 4 days of eDiary entries related to defecation per week

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- Per-Protocol Population: all randomized subjects who completed at least 81 days of the 12-week treatment period (i.e., 11 weeks and 4 days, which would be sufficient to count as 12 weeks of data) and did not have any major protocol deviations. (Major protocol deviations were defined as those that could have potentially affected the efficacy conclusions of the study and were determined prior to unblinding.)
The ITT population was the prespecified population for efficacy analyses. The ITT and mITT populations were analyzed as randomized.

Sample Size Determination

The target study population size of 540 subjects (270 subjects in the active treatment group and 270 subjects in the placebo group) was determined using an assumption of a 45% responder proportion from the naldemedine 0.2 mg group and 30% responder proportion from the placebo group for the ITT Population, which provided >95% power to detect a $\geq 15\%$ difference between groups in responder proportions with a 2-sided significance level of 0.05 by Pearson's chi-squared test.

Planned Statistical Analyses

For primary efficacy endpoint analyses, the difference in the responder proportion between the naldemedine and placebo treatment arms was analyzed using the Cochran Mantel Haenszel test, adjusted by the opioid dose strata. The 95% confidence interval (CI) was calculated for the difference between the groups' responder proportion. In addition, the 95% CIs for the responder proportions of each treatment group were calculated using the Clopper-Pearson method.

Subgroup analyses for the primary efficacy endpoint were performed for the following subgroups:

- opioid dose strata
- age
- body mass index (BMI)
- sex
- race
- region (country and site)

Results for subgroup analyses were presented descriptively.

As stated above, efficacy analyses were conducted using the ITT population as the primary analysis population, and missing data were generally handled conservatively, whereby subjects with insufficient data were defined as non-responders, as agreed upon during the End-of-Phase 2 meeting between the Applicant and the Division. In addition, six sensitivity analyses were performed for the primary endpoint to evaluate the impact of missing data, as recommended by the Agency:

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1. Observed case: Subjects were excluded from the analysis at any week if they had <4 days of eDiary entries related to defecation in that week. A subject who did not have ≥ 9 evaluable weeks was considered as a “non-responder.” The frequency of SBMs per week was defined in the same manner as the primary analysis population.
2. Complete case: Subjects were excluded from the analysis if they had <4 days of eDiary entries related to defecation at any week. The frequency of SBMs per week was defined in the same manner as the primary analysis population.
3. Worst case: If subjects had missing eDiary entries related to defecation at any day in a week, that week was considered as a “non-response” week.
4. Modified worst case: If subjects had no entries related to defecation at a day, the number of SBMs at the day was considered as worst value (i.e., 0 SBMs). Specifically, the frequency of SBMs per week was defined as total number of SBMs using only available data for that week. However, if a treatment week was non-evaluable, that week was treated as a “non-response” week.
5. Modified intent-to-treat (mITT) Population: The mITT Population was analyzed using the same methods as the primary analysis population.
6. Per-Protocol (PP) Population: The Per-Protocol Population was analyzed using the same methods as the primary analysis population.

The reader is referred to the statistical review by George Kordzakhia, Ph.D, additional details.

Protocol Amendments

Three amendments were applied to the original protocol dated 19 June 2013, all of which were issued after initiation of enrollment on 29 August 2013.

- Amendment 1: 04 October 2013
- Amendment 2: 11 June 2014
- Amendment 3: 16 October 2014

The following are the key changes made to the protocol for Study V9231:

Amendment 1

- Added clarification of BMCA inclusion criteria
- Added text to clarify eligibility criteria based on SBMs
- Changed text to clarify procedures for rescue laxative therapy
- Added text to allow for Investigator discretion on medication that may have had a significant impact on the GI system or bowel habits

Amendment 2

- Clarification that laxative therapy was allowed during the Follow-up Period
- Redefined allowable use of tramadol and tapentadol for clarity

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- Revised time points for primary efficacy endpoint analysis

Amendment 3

- Revised secondary efficacy endpoints to provide a more thorough clinical efficacy summary of naldemedine including effects from baseline to endpoint, baseline to the first week, straining, and CSBMs
- Added an exploratory endpoint to further assess the effect on SBMs without straining over time
- Removed PK assessment as an exploratory endpoint
- Changed the definition of the mITT Population to produce a population that more accurately accounted for challenges encountered by subjects required to use an electronic data capture tool
- Modified the Safety Population definition to be more inclusive in order to obtain a larger population
- Further clarified the definition of insufficient primary endpoint data and a “non-response” week

No changes were made to the planned analyses.

All protocol amendments were implemented prior to enrollment and applied to both Studies V9231 and V9232; therefore, the same study procedures were used throughout both pivotal trials.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant reported that operating procedures and audit programs were by the CRO and Applicant in accordance with the Good Clinical Practice (GCP) guidelines, as documented by the International Conference on Harmonization (ICH) and the FDA.

Financial Disclosure

None of the site investigators who participated in this clinical trial had disclosable financial information. Additional details are provided in Section 13.2.

Subject Disposition

The subject disposition for all 974 screened subjects in V9231 is shown in Figure 7. Of the 274 subjects randomized to naldemedine, 2 subjects were not dosed (vs. 0 subjects randomized to placebo):

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- Subject 12317-010 was randomized but withdrew consent prior to dosing, because the subject did not want to stay at the site for the time required to complete all study procedures for the day of randomization.
- Subject 12322-004 was randomized but discontinued from the study prior to dosing since the site staff was unable to obtain a blood sample.

Study completion rates were similar between the two V9231 treatment arms—85.0% for the naldemedine group and 87.2% for the placebo arm. The number of study discontinuations was slightly higher in the naldemedine group (n=41, 15.0%) vs. the placebo group (n=35, 12.8%).

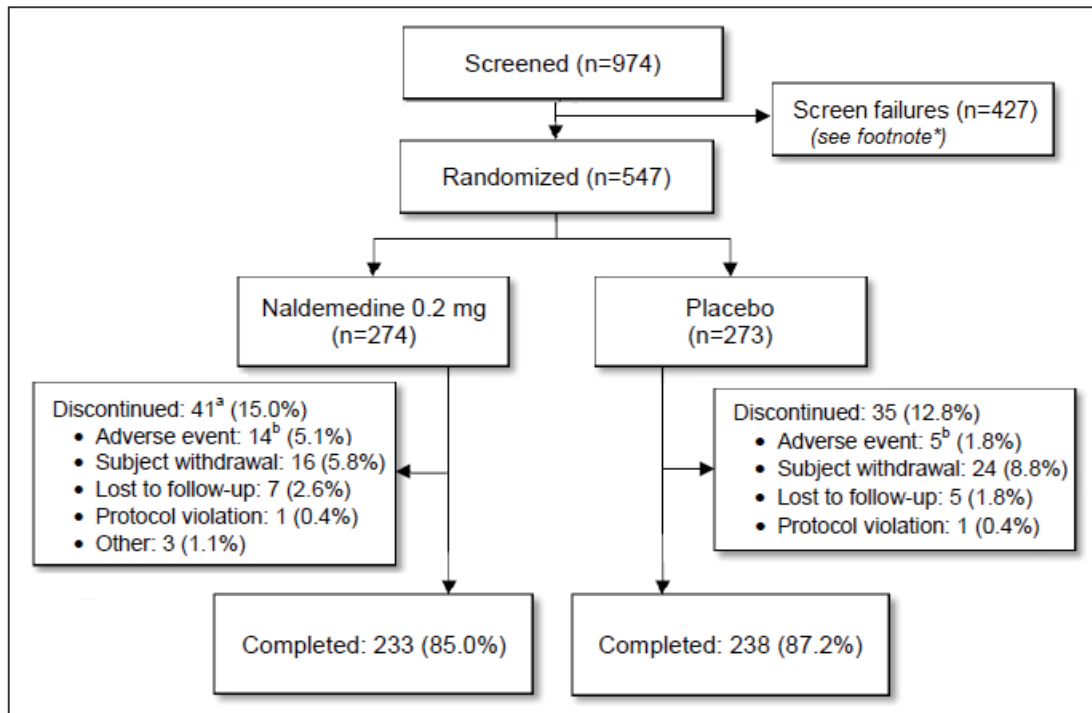
Notably, the naldemedine group had a higher proportion of subjects who discontinued due to a TEAE (n= 14, 5.1%), accounting for 34% of premature study terminations in the naldemedine arm, compared to the placebo group (n=5, 1.8%), for whom TEAE was cited as the reason for 14% of premature study terminations.

On the other hand, subject withdrawal led to premature study termination in 24 subjects (8.8%) in the placebo arm vs. 16 subjects (5.8%) in the naldemedine arm.

For both arms, discontinuation due to “withdrawal by subject” was the most common reason for premature study termination. Of these, lack of efficacy was cited as the reason for discontinuation for 2 subjects in the naldemedine group vs. 9 subjects in the placebo group. For 6 subjects (4 in the naldemedine group and 2 in the placebo group), no reason for discontinuation was specified. Numbers of subjects lost to follow-up were not notably different between groups (7 in the naldemedine group vs. 5 in the placebo group).

Study discontinuations due to TEAEs are discussed as part of the safety evaluation in Section 8. In addition, a summary of subject disposition and early study termination for all 3 controlled phase 3 studies is shown in Section 7.1.1.

Figure 6: Subject Disposition for Study V9231



(Source: Adapted from Applicant's Figure 10-1, "Consort Diagram for Subject Disposition - All Subjects Enrolled", Clinical Study Report: 1314V9231, p 61/1539; NDA 208854, Module 5.3.5.1)

^a Includes 2 subjects who were randomized but not dosed

^b Includes 1 subject discontinued due to an adverse event with an onset prior to study drug initiation

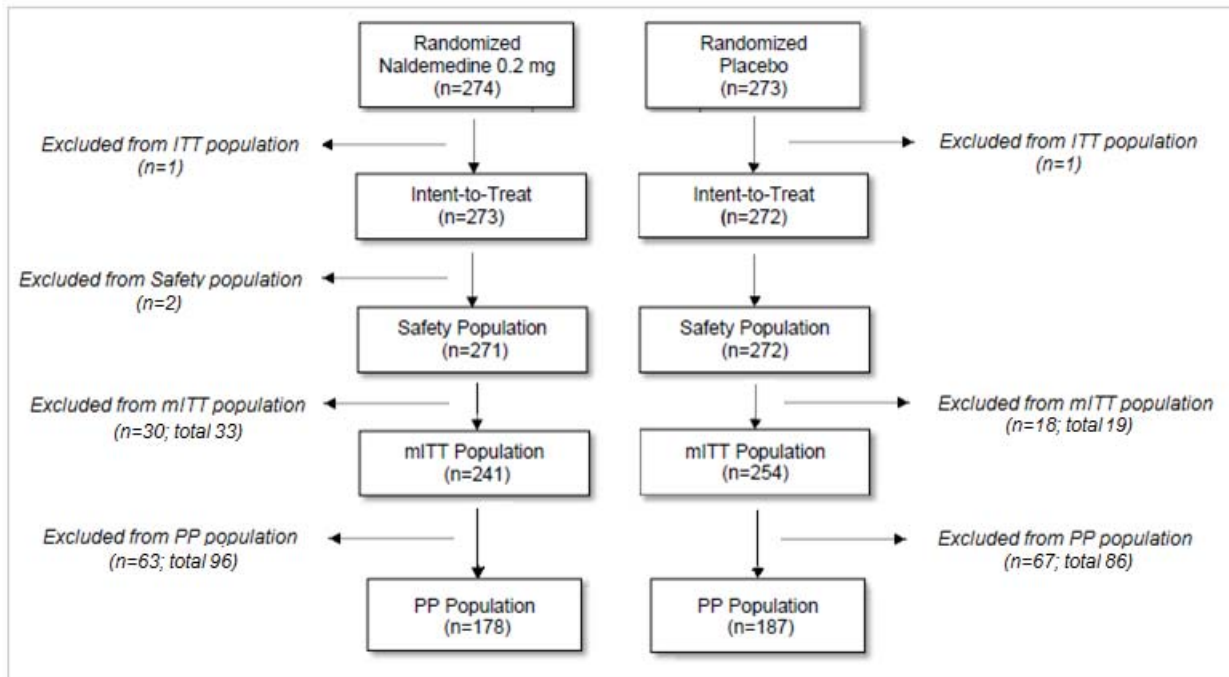
* Reasons for screen failure: (n=427)

- eDiary eligibility (n=126)
- eDiary compliance (n=48)
- Positive urine drug screen (n=17)
- Unstable laxative/opioid regimen (n=15)
- Prohibited concomitant medication (n=4)
- Screening laboratory test (n=2)
- Laboratory results (n=61)
- Medical history (n=22)
- Other (n=132)

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The analysis populations used in Study V9231 are shown in Figure 8, and the reasons for subject exclusion by the Investigator are summarized in Table 11. Overall, more subjects from the naldemedine group were excluded from any analysis population (n=96, 35.0%) vs. the placebo group (n=86, 31.5%). The largest difference between groups was the number of subjects excluded from the mITT population because <4 weeks of the study were completed with ≥4 days of diary entries per week [32 subjects excluded from the mITT population of the naldemedine arm (11.7%) vs. 18 from the placebo arm (6.6%)]. The higher number of early discontinuations in the naldemedine group due to TEAEs can account for this disparity. This is an important consideration when interpreting primary efficacy data based on the ITT population which classified subjects without minimum required data as non-responders.

Figure 7: Analysis Populations for Study V9231



(Source: Adapted from Applicant’s Figure 10-1, “Consort Diagram for Subject Disposition – All Subjects Enrolled”, Clinical Study Report: 1314V9231, page 61/1539)

Table 11: Randomized Subjects Excluded from Analysis Populations in Study V9321 (N=547)

Analysis Population	Reason for Exclusion*	Treatment Arm	
		Naldemedine (N=274)	Placebo (N=273)
ITT	Double enrollment at different study sites	1 (0.4)	1 (0.4)
Safety	No study drug administered	2 (0.7)	0
mITT	Did not complete first 4 weeks of the study with at least 4 days of diary entries/week	32 (11.7)	18 (6.6%)
PP	Any*	63 (23.0)	67 (24.5)
	Withdrawal before Day 81 of treatment period	38 (13.9)	31 (11.4)
	Use of rescue medication <60 hours after BM	31 (11.3)	32 (11.7)
	IMP Compliance <80% or >120%	22 (8.0)	16 (5.9)
	Prohibited concomitant medications/therapy	16 (5.9)	20 (7.3)
	<30 mg average opioid TDD during treatment period	2 (0.7)	0
	Incorrect study drug administered	1 (0.4)	0
	Active medical disease affecting bowel transit**	0	2 (0.7)
Total	All Excluded	96 (35.0)	86 (31.5)

(Source: Reviewer's based on Applicant's Figure 10-1, "Consort Diagram for Subject Disposition – All Subjects Enrolled", Clinical Study Report: 1314V9231, page 61/1539; Analysis datasets, NDA 208854, Module 5.3.5.1)

Abbreviations used in table: BM, bowel movement; IMP, investigational medicinal product; ITT, intent-to-treat; mg, milligrams; mITT, modified intent-to-treat; PP, per protocol; TDD, total daily dose

*Excluded subjects may have had ≥ 1 protocol deviation resulting in exclusion

** i.e., ileus, uncontrolled hypothyroidism, irritable bowel syndrome (IBS), inflammatory bowel disease, fecal incontinence

Protocol Violations/Deviations

A total of 265 major protocol violations were reported for randomized subjects in Study V9231—145 in the naldemedine group and 120 in the placebo group—and are summarized in Table 11 and Table 12.

At least 1 major protocol deviation was reported for 182 subjects (96 subjects in the naldemedine group and 86 subjects in the placebo group). As discussed in the previous section, the difference between treatment arms is primarily due to the higher percentage of subjects in the naldemedine arm without the minimum required efficacy data. Compared to placebo, the naldemedine group had 5% more subjects without ≥ 4 weeks of data (i.e., mITT violation) and an additional 2.5% more subjects who withdrew before Day 81 of treatment period (PP violation), which can be attributed, in large part, to the higher rate of TEAE-related early discontinuations among naldemedine-treated subjects.

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Table 12: Major Protocol Deviations in Study V9231

Protocol Deviation Category	Naldemedine (N=274)	Placebo (N=273)
Treatment deviation	52 (19.0)	43 (15.8)
Inappropriate rescue medication use	31 (11.3)	32 (11.7)
Prohibited concomitant medication	16 (5.8)	20 (7.3)
Enrollment error	1 (0.4)	1 (0.4)
Exclusion Criteria	0	2 (0.7)
Administrative error	1 (0.4)	0

(Source: Reviewer's table based on analysis datasets, NDA 208854, Module 5.3.5.1)

Demographic and Baseline Characteristics

Overall, the treatment arms in Study V9231 were well-balanced with respect to demographics, prior medical history, and concomitant medical conditions and treatments. Baseline disease-related characteristics were also similar between groups.

Subject Demographics

Subject demographics for the ITT population for Study V9231 are summarized in Table 13, with a breakdown of the ITT population and clinical sites by country of origin shown in Table 14.

Although the mean and median age of the treatment groups were similar, there were 17% fewer subjects aged ≥65 years old in the naldemedine treatment group than the placebo group. This is notable because this demographic group is also at risk for age-related idiopathic constipation, which may confound treatment response. In both groups, the numbers of subjects with age ≥75 years old were small (6 in the naldemedine group and 8 in the placebo group).

Notably, mean and median body mass index (BMI) of the study population were in the obese range (31.3 kg/m² and 30.3 kg/m², respectively), and 55% of study subjects had a BMI in the obese range. Average BMI values and BMI distribution were similar between treatment arms. The high prevalence of obesity in this population is reflective of the high overall morbidity of this patient population and is likely a good representation of the post-marketing treatment population.

Of the clinical trials sites who participated in Study V9231, 70% were in the United States, and enrollment at these sites accounted for 82% of the subjects in the V9231 ITT population.

Table 13: Demographics for Subjects in Study V9321, ITT Population

Demographic Parameter		Naldemedine (N=273)	Placebo (N=272)	Total (N=545)
Age (years)	n	273	272	545
	Mean ± SD	53.3 ± 10.4	53.4 ± 11.0	53.4 ± 10.7
	Median	53.0	53.0	53.0
	Range	19 – 79	26 – 78	19 – 79
Age Category (years), n (%)	<40	25 (9.2)	26 (9.6)	51 (9.4)
	>=40 to <65	209 (76.6)	199 (73.2)	408 (74.9)
	>=65	39 (14.3)	47 (17.3)	86 (15.8)
	>=75	6 (2.2)	8 (2.9)	14 (2.6)
Sex n (%)	Male	112 (41.0)	104 (38.2)	216 (39.6)
	Female	161 (59.0)	168 (61.8)	329 (60.4)
Height (cm)	n	272	271	271 543
	Mean ± SD	168.8 ± 10.0	169.3 ± 10.2	169.0 ± 10.1
	Range	149.9 – 188.1	142.0 – 169.0	142.0 – 188.1
BMI (kg/m ²)	n	272	271	543
	Mean ± SD	31.4 ± 7.4	31.3 ± 6.8	31.3 ± 7.1
	Median	30.4	30.3	30.3
	Range	18.7 – 57.1	16.7 – 63.8	16.7 – 63.8
BMI Category (kg/m ²), n (%)	<18.5	0	1 (0.4)	1 (0.2)
	>=18.5 to <25.0	55 (20.1)	54 (19.9)	109 (20.0)
	>=25.0 to <30.0	69 (25.3)	64 (23.5)	133 (24.4)
	>=30.0	148 (54.2)	152 (55.9)	300 (55.0)
	Missing	1 (0.4)	1 (0.4)	2 (0.4)
Race, n (%)	American Indian or Alaska Native	1 (0.4)	1 (0.4)	2 (0.4)
	Asian	2 (0.7)	1 (0.4)	3 (0.6)
	Black	53 (19.4)	48 (17.6)	101 (18.5)
	Native Hawaiian or Other Pacific Islander	1 (0.4)	2 (0.7)	3 (0.6)
	White	216 (79.1)	220 (80.9)	436 (80.0)
Ethnicity, n (%)	Hispanic or Latino	26 (9.5%)	27 (9.9%)	53 (9.7%)
	Not Hispanic/Latino	247 (90.5)	245 (90.1)	492 (90.3)

(Source: Reviewer's table adapted from Applicant's Table 2, "Demographic and Baseline Characteristics – Intent-to-Treat Population", Clinical Study Report: 1314V9231, pages 67-70/1539)

Abbreviations used in table: %, percentage; BMI, body mass index; cm, centimeter; ITT, intent-to-treat; kg, kilogram; m², square meters; n, number of subjects; SD, standard deviation

Table 14: Countries of Origin for Clinical Sites and Subject, Studies V9321 and V9232- ITT Populations

	Study V9231			Study V9232		
	Clinical Sites (N=68)	Subjects (N=545)		Clinical Sites (N=69)	Subjects (N=550)	
		Naldemedine (N=273)	Placebo (N=272)		Naldemedine (N=276)	Placebo (N=274)
United States	48 (70.6)	230 (84.2)	229 (84.2)	54 (78.3)	241 (87.3)	239 (87.2)
United Kingdom	8 (11.8)	15 (5.5)	14 (5.1)	0	0	0
Czech Republic	4 (5.9)	15 (5.5)	16 (5.9)	6 (8.7)	15 (5.4)	14 (5.1)
Poland	3 (4.4)	2 (0.7)	2 (0.7)	3 (4.3)	7 (2.5)	8 (2.9)
Germany	2 (2.9)	6 (2.2)	6 (2.2)	4 (5.8)	6 (2.2)	7 (2.6)
Austria	2 (2.9)	2 (0.7)	2 (0.7)	1 (1.5)	1 (0.4)	1 (0.4)
Spain	1 (1.5)	3 (1.1)	3 (1.1)	1 (1.5)	6 (2.2)	5 (1.8)

(Source: Reviewer's table based on analysis data, NDA 208854, Module 5.3.5.1)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

- **Baseline SBM Frequency**

Mean frequency of SBMs at baseline for both treatment arms of the V9231 ITT population was 1.3 ± 0.7 SBM/week, ranging between 0 to 2.5 SBM/week. Both groups also had similar distribution of baseline SBM frequency (Table 15). No subjects had a weekly SBM frequency of ≥ 3 SBM/week, consistent with the eligibility criteria used to establish a diagnosis of OIC. The severity of other baseline constipation-related characteristics and symptoms were also similar between groups.

Table 15: Baseline Weekly Frequency of Spontaneous Bowel Movements in the ITT Population, Study V9231 (N=545)

		Naldemedine 0.2 mg (N=273)	Placebo (N=272)	Total (N=545)
Statistics	Mean $\pm$ SD	1.3 ± 0.7	1.3 ± 0.7	1.3 ± 0.7
	Median	1.5	1.5	1.5
	Range	0 – 2.5	0 – 2.5	0 – 2.5
SBM/week, n (%)	<1	69 (25.3)	71 (26.1)	140 (25.7)
	≥ 1 to <2	116 (42.5)	111 (40.8)	227 (41.7)
	≥ 2 to <3	88 (32.2)	90 (33.1)	178 (32.7)
	≥ 3	0	0	0

(Source: Adapted from Applicant's Table 10-3, "Spontaneous Bowel Movements per Week at Baseline – Intent-to-Treat Population", Clinical Study Report: 1314V9231, page 71/1539)

Abbreviations used in table: ITT, intent-to-treat; n, number; SBM, spontaneous bowel movement

• Baseline Opioid Use

Baseline opioid use for the ITT population of Study V9231 was assessed during the 14-day Screening Period. For each subject, a baseline mean total daily dose (TDD) of opioids was calculated and expressed in morphine equivalents based on standard conversion factors. Baseline opioid TDD data are shown in Table 16.

The mean TDD of opioid was ~15 mg (morphine equivalents) higher for the placebo group than the naldemedine group, though the median dose was the same for both groups. This difference was driven by the higher percentage of patients receiving average doses >400 mg morphine equivalents/day (5.5% vs. 3.3%). When the mean daily dose at baseline was calculated for subjects taking up to 400 mg, no difference between groups was observed.

In addition, 5 of the 6 patients with mean TDD below the minimum required dose of 30 mg morphine equivalents/day were in the placebo arm. In spite of these differences, the distribution of opioid doses were similar between >95% of the subjects in both 2 treatment arms, making it unlikely that these differences had a significant impact on efficacy results.

Table 16: Baseline Total Daily Dosage (TDD) of Opioid Medication (mg Morphine Equivalents) in the ITT Population, Study V9231 (N=545)

Opioid TTD (Morphine Equivalents)		Naldemedine (N=273)	Placebo (N=272)	Total (N=545)
Dose (mg)	Mean ± SD	125.2 ± 118.0	139.7 ± 153.7	132.4 ± 137.0
	Median	90.0	90.0	90.0
	Min – Max	0 – 730.0	7.5 – 1080.0	0 – 1080.0
	Q1 – Q3	40.0 – 1080.0	40.0 – 1080.0	40.0 – 1080.0
Dose Categories (mg), n (%)	<30	5 (1.8)	1 (0.4)	6 (1.1)
	>=30 to <=100	148 (54.2)	145 (53.3)	293 (53.8)
	>100 to <=200	68 (24.9)	72 (26.5)	140 (25.7)
	>200 to <=400	43 (15.8)	39 (14.3)	82 (15.0)
	>400	9 (3.3)	15 (5.5)	24 (4.4)

(Source: Adapted from Applicant's Table 10-4, "Average Total Daily Dose of Opioid at Baseline: Electronic Data Capture Data – Intent-to-Treat Population", Clinical Study Report: 1314V9231, page 72/1539)

Abbreviations used in table: %, percentage; ITT, intent-to-treat; mg, milligrams; Max, maximum; Min, minimum; n, number of subjects; Q1, quartile 1; Q2, quartile 2; SD, standard deviation; TDD, total daily dose

Opioid medications used by subjects in the ITT population of Study V9231 were similar in both treatment arms, including use of tramadol and tapentadol (analgesics with dual mechanisms of action, considered weak opioids).

Table 17: Opioid Medications in the ITT Population of Study V9231 (N=545)

	Naldemedine (N=273)	Placebo (N=272)
Oxycodone	145 (53.1)	143 (52.6)
Hydrocodone	76 (27.8)	71 (26.1)
Morphine	59 (21.6)	59 (21.6)
Fentanyl	19 (7.0)	24 (8.8)
Hydromorphone	11 (4.0)	18 (6.6)
Methadone	13 (4.8)	16 (5.9)
Codeine	9 (3.3)	11 (4.0)
Oxymorphone	10	8 (2.9)
Tramadol	9 (3.3)	8 (2.9)
Dihydrocodeine	1 (0.4)	2 (0.7)
Meperidine	1 (0.4)	0
Tapentadol	0	1 (0.4)

(Source: Reviewer's Table)

➤ **Other Concomitant medications**

Non-opioid analgesics

In addition to opioids, 115 subjects (42%) in the naldemedine group and 110 subjects (40%) in the placebo group were receiving ≥ 1 non-opioid pain medication (Table 18). The most class of non-opioid analgesics in both groups were GABA analogues, such as gabapentin and pregabalin, and non-steroidal anti-inflammatory drugs (NSAIDs). Use of NSAIDs, a class of medications with common adverse effect of constipation, was higher in the placebo group (31.5%, vs. 27.8% in the naldemedine arm).

Table 18: Concomitant Non-Opioid Analgesics in the ITT Population, Study V9231 (N=545)

Analgesic Medication Class	Naldemedine (N=273)	Placebo (N=272)
GABA analogues (e.g., gabapentin, pregabalin, topiramate)	89 (32.6)	89 (32.7)
Non-Steroidal Anti-inflammatory Drugs	76 (27.8)	86 (31.5)
Anilides (e.g., acetaminophen)	26 (9.5)	19 (7.0)
Salicylic Acid And Derivatives	13 (4.8)	12 (4.4)
COX-2 Inhibitors	8 (2.9)	8 (2.9)

(Source: Reviewer's table based on analysis data, NDA 208854, Module 5.3.5.1)

Abbreviations used in table: COX, cyclooxygenase; GABA, gamma-aminobutyric acid

Concomitant Medications (Excluding Analgesics and Laxatives)

Classes of medications used by $\geq 5\%$ of subjects in Study V9231 are shown in Table 19. Concomitant medication use was generally similar between groups. In both groups, the most common classes of concomitant medications (excluding analgesics and laxatives) were

centrally acting muscle relaxants (e.g., tizanidine, baclofen, cyclobenzaprine, carisoprodol, etc.) and benzodiazepines.

One notable difference is the higher rate of use of selective serotonin reuptake inhibitors (SSRIs), a class of medications with common side effect of constipation, among subjects in the placebo arm (21.3%, vs. 15.0% in the naldemedine arm). In the naldemedine arm, usage of beta adrenergic blockers was greater (19.7%, vs. 15.4% in placebo).

Table 19: Classes of Medications with Reported Use in ≥5% of the ITT Population of Study V9231 (Excluding Analgesics and Laxatives)

Medication Class	Naldemedine (N=273)	Placebo (N=272)
Muscle Relaxants, Centrally Acting	94 (34.4)	99 (36.4)
Benzodiazepines	86 (31.5)	86 (31.5)
HMG CoA Reductase Inhibitors	70 (25.6)	85 (31.3)
Proton Pump Inhibitors	62 (22.7)	69 (25.4)
ACE Inhibitors	65 (23.8)	57 (21.0)
Selective Serotonin Reuptake Inhibitors	41 (15.0)	58 (21.3)
Beta Adrenergic Blockers	54 (19.7)	42 (15.4)
Platelet Aggregation Inhibitors, including aspirin	41 (15.0)	49 (18.0)
Serotonin–Norepinephrine Reuptake Inhibitors	47 (17.2)	41 (15.0)
Calcium Channel Blockers	42 (15.4)	44 (16.2)
Inhaled Beta-2-Adrenoreceptor Agonists	37 (13.6)	43 (15.8)
Antibiotics, Systemic (Oral)	34 (12.5)	34 (12.5)
Blood Glucose Lowering Agents (Except Insulin)	36 (13.2)	31 (11.4)
Thiazide Diuretics	33 (12.1)	33 (12.1)
Multivitamins	31 (11.4)	36 (15.8)
Thyroid Hormones	29 (10.6)	37 (13.6)
Systemic Antihistamines	34 (12.5)	31 (11.4)
Monoamine Reuptake Inhibitors	25 (9.2)	32 (11.8)
Vitamin D And Analogues	28 (10.3)	25 (9.2)
Other Antidepressants (Trazodone and Remeron)	24 (8.8)	27 (9.9)
Sedative Hypnotic Sleep Agents	25 (9.2)	25 (9.2)
Inhaled Corticosteroids	23 (8.4)	25 (9.2)
Angiotensin II Antagonists	22 (8.1)	17 (6.2)
Fish Oil/Omega Fatty Acids	22 (8.1)	16 (5.9)
Loop Diuretics	20 (7.3)	18 (6.6)
Topical Anesthetics (Amides)	17 (6.2)	19 (7.0)
Bupropion	13 (4.8)	16 (5.9)
Intranasal Corticosteroids	18 (6.6)	10 (3.7)
Estrogens	12 (4.4)	17 (6.2)
Histamine-2-Receptor Antagonists	11 (4.0)	17 (6.2)

(Source: Reviewer's table based on analysis data, NDA 208854, Module 5.3.5.1)

Abbreviations in table: ACE, angiotensin converting enzyme; HMG CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A

- Concomitant medical conditions and medical history

Causes of non-cancer pain

Table 17 lists the underlying etiology of non-cancer pain reported in >2% of the ITT population in Study V9231. By far, the most common source of pain was back pain, reported by 64.1 and 59.9% of subjects in the naldemedine and placebo arms, respectively. Overall, the types of pain reported by subjects were similar between treatment arms.

Table 20: Cause of Non-Cancer Pain Reported by ≥2% of the ITT Population, Study V9231

Medical Condition	n (%)		
	Naldemedine (N=273)	Placebo (N=272)	Total (N=545)
Back Pain	175 (64.1)	163 (59.9)	338 (62.0)
Neck Pain	27 (9.9)	18 (6.6)	45 (8.3)
Osteoarthritis	18 (6.6)	11 (4.0)	29 (5.3)
Pain	11 (4.0)	18 (6.6)	29 (5.3)
Arthralgia	13 (4.7)	15 (5.5)	28 (5.1)
Intervertebral Disc Compression/Degeneration	8 (2.9)	12 (4.4)	20 (3.7)
Fibromyalgia	7 (2.6)	10 (3.7)	17 (3.2)
Musculoskeletal Pain	8 (2.9)	9 (3.3)	17 (3.2)
Post Laminectomy Syndrome	7 (2.6)	9 (3.3)	16 (2.9)
Pain In Extremity	9 (3.3)	5 (1.8)	14 (2.6)
Intervertebral Disc Displacement/Protrusion	5 (1.8)	8 (2.9)	13 (2.4)
Spinal Osteoarthritis/Spondylolysis	6 (2.2)	5 (1.8)	11 (2.0)

(Source: Reviewer's table based on analysis data, NDA 208854, Module 5.3.5.1)

Medical History: General

The most common medical conditions among subjects in Study V9231, occurring in >1/3 of ITT population of both treatment arms, were back pain (also the most commonly reported cause of subjects' non-cancer pain), hypertension, depression, dyslipidemia, and anxiety. All medical conditions reported in at least 10% of the ITT population are listed in Table 20.

Table 21: Medical Conditions Reported in >10% of Subjects in the ITT Population, Study V9231

	Naldemedine (N=273)	Placebo (N=272)	Total (N=545)
Back Pain	196 (71.8)	184 (67.6)	380 (69.7)
Hypertension	140 (51.3)	128 (47.1)	268 (49.2)
Depression	117 (42.9)	114 (41.9)	231 (42.4)
Dyslipidemia	103 (37.7)	115 (42.3)	218 (40.0)
Anxiety/Anxiety Disorder	94 (34.4)	98 (36.0)	192 (35.2)
Insomnia	90 (33.0)	80 (29.4)	170 (31.2)
Osteoarthritis	67 (24.5)	72 (26.5)	139 (25.5)

	Naldemedine (N=273)	Placebo (N=272)	Total (N=545)
Gastroesophageal Reflux Disease	67 (24.5)	72 (26.5)	139 (25.5)
Menopause/Postmenopause	65 (23.8)	73 (26.8)	138 (25.3)
Headache/Migraine	70 (25.6)	63 (23.2)	133 (24.4)
Hysterectomy	63 (23.1)	68 (25.0)	131 (24.0)
Drug Hypersensitivity	45 (16.5)	62 (22.8)	107 (19.6)
Muscle Spasms	55 (20.1)	51 (18.8)	106 (19.4)
Neck Pain	57 (20.9)	41 (15.1)	98 (18.0)
Intervertebral Disc Displacement/Protrusion	44 (16.1)	50 (18.4)	94 (17.2)
Seasonal Allergy	52 (19.0)	39 (14.3)	91 (16.7)
Arthralgia	38 (13.9)	46 (16.9)	84 (15.4)
Diabetes Mellitus	43 (15.8)	41 (15.1)	84 (15.4)
Intervertebral Disc Compression/Degeneration	30 (11.0)	49 (18.0)	79 (14.5)
Asthma/Bronchospasm	39 (14.3)	40 (14.7)	79 (14.5)
Spinal Fusion/Surgery	41 (15.0)	35 (12.9)	76 (13.9)
Hypothyroidism	29 (10.6)	40 (14.7)	69 (12.7)
Cholecystectomy	34 (12.5)	34 (12.5)	68 (12.5)
Spinal Osteoarthritis/Spondylolysis	38 (13.9)	28 (10.3)	66 (12.1)
Fibromyalgia	28 (10.3)	27 (9.9)	55 (10.1)

(Source: Reviewer's table)

Hypothyroidism was more common among placebo-treated subjects (14.7%) than naldemedine subjects (10.6%), consistent with the higher frequency of thyroid hormone replacement among subjects in the naldemedine arm. Although hypothyroidism is strongly associated with constipation, this disparity is unlikely to be a confounder because control of hypothyroidism was a prerequisite for study participation. It should be noted, however, that the same imbalance in favor of the naldemedine arm also occurred in Study V9232 (See Section 6.2.2).

In the naldemedine arm, hypertension was more common (53.6%, compared to placebo 45.3%; difference 8.3%). This is an important consideration for analyses of hypertension-related TEAE and vital sign data, particularly because there is a plausible mechanism for increased blood pressure with PAMORA treatment. It is important to note, however, that the same imbalance in favor of the placebo arm occurred in Study V9232. Also of note, seasonal allergy was more frequent among naldemedine subjects, but the rate systemic antihistamine use was substantially higher among the subjects in this treatment arm.

For both groups, hypertension was the 2nd most common medical condition in the ITT population (~50% of subjects), with higher rate among subjects in the naldemedine group (51.3%, vs. 47.1% of placebo subjects; difference 4.2%). On the other hand, the incidence of dyslipidemia, also in the top 5 most common medical conditions for both groups, was lower in the naldemedine group (37.7%, vs. 42.3% in the placebo group; difference -4.6%).

Similarly, the incidence of two important cardiovascular conditions of interest was also lower in the naldemedine group, specifically:

- Myocardial infarction in 5 subjects in the naldemedine group (1.8%) vs. 10 subjects in the placebo group (3.7%),
 - “Myocardial ischemia” was reported for 3 additional subjects in the placebo group (0 in the naldemedine group); combined incidence of myocardial infarction/ischemia in the placebo group was 4.8%
- Coronary artery disease in 7 subjects in the naldemedine group (2.6%) vs. 18 subjects in the placebo group (6.6%)
 - 1 subject in each group had a diagnosis of “arteriosclerosis”

Overall, peripheral arterial disease was rare (total 6 subjects), but the incidence was disproportionately higher in the naldemedine group [n=5 (1.8%) vs. n=1 (0.4%) in the placebo group].

The group differences for these cardiac conditions and cardiovascular risk factors are important to this application due to their relevance to MACE assessments (see Section 8.5.1), but were unlikely to have impacted efficacy results.

Also relevant to the safety review was the difference in respiratory conditions between groups. Overall, 98 subjects in the placebo group (36.0%) reported ≥1 respiratory condition, vs. 81 in the naldemedine group (29.7%, difference 6.3%). Specifically, COPD, including emphysema and chronic bronchitis, was more common in the placebo group (n=32; 11.7%), compared to the naldemedine group (n=18, 6.6%). The incidence of sleep apnea was higher in the placebo group (11.0%, vs. 8.4% in the naldemedine group). The rates of other respiratory conditions, including asthma and allergic rhinitis/sinusitis, were similar between groups.

In the naldemedine group, history of neck pain was more common (20.9%, vs. 15.1% in the placebo group). This finding is relevant for interpretation of AE data, in which neck pain occurred more frequently in the naldemedine group (see Section 8.4.5).

In general, the incidence of mood disorders, nervous system disorders, cardiovascular disease, diabetes, renal disease, and hepatobiliary disorders were similar between groups.

Study Compliance

- Treatment Compliance- Study Drug

Study drug compliance rates were similar between treatment groups. Mean compliance with study drug during the Treatment Period of Study V9231 was 96.7% for the naldemedine group and 98.6% for the placebo group.

- Treatment Compliance- Study Drug Diary completion

Seventy-three subjects had ≥ 1 week with non-evaluable efficacy data (i.e., data for < 4 of 7 days)—38 in the naldemedine group and 35 in the placebo group. Of these, only 7 active subjects (3 naldemedine- and 4 placebo-treated subjects) had non-evaluable data for ≥ 3 study weeks, suggesting overall good eDiary compliance during study participation.

Efficacy Results – Primary Endpoint

Treatment response (i.e., “responder”) was defined as ≥ 9 positive-response weeks out of the 12-week Treatment Period and ≥ 3 positive-response weeks out of the last 4 weeks of the 12-week Treatment Period, where a positive-response week was defined as ≥ 3 SBMs per week and an increase from baseline of ≥ 1 SBM per week for that week.

The proportion of responders by treatment group and the between-group comparisons for the ITT Population are summarized in Table 22. The proportion of SBM responders in the naldemedine group was 47.6% vs. 34.6% in the placebo group, for which the treatment difference (13.0%) was statistically significant ($p < 0.002$) and 95% confidence intervals for group responder rates did not overlap. (Table 21) Also, similar treatment differences were observed when treatment groups were analyzed by opioid dose strata—13.1% and 13.0% for the lower and higher dose strata, respectively (Table 22) and only a small (3%) difference in response rates was observed between opioid dose strata for both treatment arms.

Table 22: Primary Efficacy Analysis: Difference in Proportion of Responders, Study V9231 (ITT Population)

		Naldemedine (N=273)	Placebo (N=272)
Proportion of Responders	% (n/N)	47.6 (130/273)	34.6 (94/272)
	95% CI (%)	41.6, 53.7	28.9, 40.5
Comparison between arms (Naldemedine vs. Placebo)	Difference of Proportions (%)	13.0	
	95% CI (%)	4.8, 21.3	
	p-value	0.0020	

(Source: Reviewer’s table, adapted from Applicant’s Table 11-1, “Proportion of Responders: Primary Analysis – Intent-to-Treat Population”, Clinical Study Report: 1314V9231, page77/1539)

Abbreviations used in table: %, percentage; CI, confidence interval

Table 23: Difference in Proportion of Responders by Opioid Dose Strata, Study V9221 (ITT Population)

Opioid Dose strata (mg*)	Treatment Arm, % (n/N)		Difference of Proportions (Naldemedine-Placebo, %)
	Naldemedine (N=273)	Placebo (N=272)	
30-100	49.0 (75/155)	35.9 (55/153)	13.1
>100	45.8 (54/118)	32.8 (39/119)	13.0

(Source: Reviewer’s Table)

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Results for all 6 primary endpoint sensitivity analyses were consistent with the primary analysis of the primary endpoint (ITT population). In each case, the proportion of responders in the naldemedine group was higher than in the placebo group with statistically significant differences between groups (p-value range 0.0001 to 0.0220, where the highest p-value is for the “Worst Case” analysis). These results support that pre-specified definitions for evaluable data and methods for handling missing data did not significantly impact primary endpoint analyses.

Of the 6 sensitivity analyses, the “modified worst case” analysis is the one that best addresses the risk of bias due to correction of weekly BM event frequencies (i.e., adjustment based on the number of completed diary entries for the week). As shown in Table 23, the modified worst case analysis of primary endpoint data yielded very similar results to the primary (ITT population) analysis. With use of uncorrected SBM frequencies for the modified worst case analysis, the responder classification for only 1 of the 545 subjects in the ITT population differed from the primary analysis classification.

Not surprisingly, the response rates for both groups are highest for the per protocol (PP) analysis population which included all subjects enrolled through Study Day 81. Therefore, all discontinuations prior to Study Day 81 were excluded from the PP population analysis, compared to the primary analysis of the ITT population, in which these subjects were classified non-responders. Because the rates of study discontinuations were similar between groups, response rates for both groups were similarly affected by missing data.

However, a shorter duration of efficacy data (minimum 4 weeks) was required for inclusion in the mITT population. Because TEAE-related discontinuations in the naldemedine group tended to occur early in treatment, the largest treatment difference was measured using the mITT population (17.2% difference between groups; 95% CI 8.6 to 25.1). A similar effect was seen for the Complete Case analysis.

Overall, these mITT and PP sensitivity analyses suggest results of the primary analysis may underestimate the magnitude of treatment effect of naldemedine due to the conservative methods for handling missing data. Although tolerability is an important factor in the overall benefit-risk assessment of the drug, the interpretation of efficacy data needs to take into account the impact of these dropouts on primary analyses.

Table 24: Sensitivity Analyses for Primary Efficacy Analyses, Study V9231

	Parameter	Treatment Arm		Difference of Proportions	
		Naldemedine (N=273)	Placebo (N=272)	Nald-Placebo, % 95% CI	<i>p</i> -value
Primary Analysis [ITT Population] (N=545)	N	273	272	13.0 (4.8, 21.3)	0.0020
	n	130	94		
	%	47.6	34.6		
Observed Case (N=545)	N	273	272	13.4 (5.2, 21.6)	0.0015
	n	131	94		
	%	48.0	34.6		
Complete Case (N=434)	N	214	220	17.0 (7.7, 26.3)	0.0004
	n	121	87		
	%	56.5	39.5		
Worst Case (n=545)	N	273	272	9.4 (1.4, 17.4)	0.0220
	n	110	84		
	%	40.3	30.9		
Modified Worst Case (N=545)	N	273	272	12.7 (4.5, 20.9)	0.0026
	n	129	94		
	%	47.3	34.6		
mITT (N=495)	N	241	254	17.2 (8.6, 25.9)	0.0001
	n	127	90		
	%	52.7	35.4		
PP (N=366)	N	179	187	14.9 (4.7, 25.1)	0.0045
	n	101	78		
	%	56.7	41.7		

(Source: Reviewer's table)

Abbreviations used in table: ITT, intent-to-treat; Nald, naldemedine; mITT, modified intent-to-treat; PP, per protocol

Data Quality and Integrity – Reviewers' Assessment

Overall, the quality of naldemedine safety and efficacy data was adequate to conduct the necessary benefit-risk assessments for this application. Despite comments by the Applicant describing challenges faced with respect to eDiary compliance, the integrity of efficacy data from self-reported efficacy assessments did not seem to be compromised by missing eDiary data, a finding which is supported by the sensitivity analyses of the primary efficacy endpoint.

For one domain, opioid medication doses, the accuracy of data collected during all phases of the study (i.e., data collected at screening, during baseline assessments, and throughout study treatment) were deemed unreliable. This reviewer's judgment was based upon findings of discrepant data between investigator (EDC)- and patient (eDiary)-reported opioid doses and unusually high variability and deviant values among individual subjects' doses. In an effort to

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address this problem, the Applicant conducted analyses excluding patients they identified discrepant EDC and eDiary data during the treatment period; however, this strategy for analyses was minimally helpful because the Applicant did address any discrepancies among baseline data. The limited usefulness of opioid dose data impacted a broad range of efficacy and safety analyses based on these data because opioid doses information was used both a disease-related characteristic for stratification and subgroup risk assessment, as well as a measure of opioid analgesia. Yet, despite the scope of analyses affected by these data as noted throughout this review, the overall determinations of naldemedine safety and efficacy to support marketing approval were not significantly impacted by this issue. However, this experience underscores the challenges of collecting detailed opioid usage data during clinical trials.

Efficacy Results – Secondary endpoints

Four secondary efficacy endpoints were predefined for Study V9231.

1. Change in the frequency of spontaneous bowel movements per week from baseline to the last 2 weeks of the treatment period
2. Change in the frequency of spontaneous bowel movements per week from baseline to week 1 of the treatment period
3. Change in the frequency of complete spontaneous bowel movements (CSBM) per week from baseline to the last 2 weeks of the treatment period
4. Change in the Frequency of Spontaneous Bowel Movements without Straining per Week from Baseline to the Last 2 Weeks of the Treatment Period

Consistent with primary endpoint analyses, the ITT population was designated as the primary analysis population for secondary endpoint analyses.

For each of the 4 key secondary endpoints, the mean increase in BM event frequency from baseline to the specified analysis timepoint was greater in the naldemedine arm vs. the placebo arm. Results were statistically significant for all 4 secondary endpoints. Similar to the primary endpoint, the data analyses of the secondary endpoints provided by the Applicant were conducted using pro-rated weekly BM event frequencies. The review team also requested additional post-hoc analyses that were based on unadjusted BM event frequencies. For both unadjusted and adjusted data, secondary endpoints are summarized in Table 24.

Treatment differences calculated based on adjusted data were consistently greater than those based on unadjusted data. Compared to unadjusted data, use of adjusted data resulted in inflated treatment differences between arms exclusively favoring the naldemedine group. Although the use of data adjustment is not statistically important (i.e., calculated p-values for treatment differences based on unadjusted data are <0.0001 to 0.0012), results based on unadjusted data are considered less biased. This reviewer acknowledges that missing data could result in underestimation of BM event frequencies based on unadjusted data (i.e., BM event frequencies based only on observed events). Therefore, this reviewer recommends that

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any secondary endpoint data included in mean BM event frequencies reported in the efficacy section of the prescribing information should be calculated exclusively using unadjusted data.

Table 25: Secondary Endpoint Analyses, ITT Population, Study V9231

Statistical Method	Secondary Endpoint (Frequency per Week)	Treatment Arm, LS Mean (SE)		Difference LS Means (Naldemedine-Placebo)	
		Naldemedine (N=573)	Placebo (N=572)	Difference 95% CI	p-value
Adjusted BM Frequency	Change in SBM: Baseline to Last 2 Weeks	3.42 (0.193)	2.12 (0.192)	1.30 (0.77, 1.83)	<0.0001
	Change in SBM: Baseline to Week 1	3.48 (0.185)	1.36 (0.184)	2.11 (1.60, 2.63)	<0.0001
	Change in CSBM: Baseline to Last 2 Weeks	2.58 (0.170)	1.57 (0.170)	1.01 (0.54, 1.48)	<0.0001
	Change in SBM without Straining: Baseline to Last 2 Weeks	1.46 (0.141)	0.73 (0.140)	0.73 (0.34, 1.12)	0.0003
Unadjusted BM Frequency	Change in SBM: Baseline to Last 2 Weeks	3.09 (0.179)	2.04 (0.178)	1.05 (0.55, 1.54)	<0.0001
	Change in SBM: Baseline to Week 1	3.29 (0.174)	1.31 (0.173)	1.98 (1.50, 2.46)	<0.0001
	Change in CSBM: Baseline to Last 2 Weeks	2.30 (0.151)	1.53 (0.150)	0.77 (0.35, 1.19)	0.0003
	Change in SBM without Straining: Baseline to Last 2 Weeks	1.30 (0.127)	0.72 (0.126)	0.58 (0.23, 0.93)	0.0012

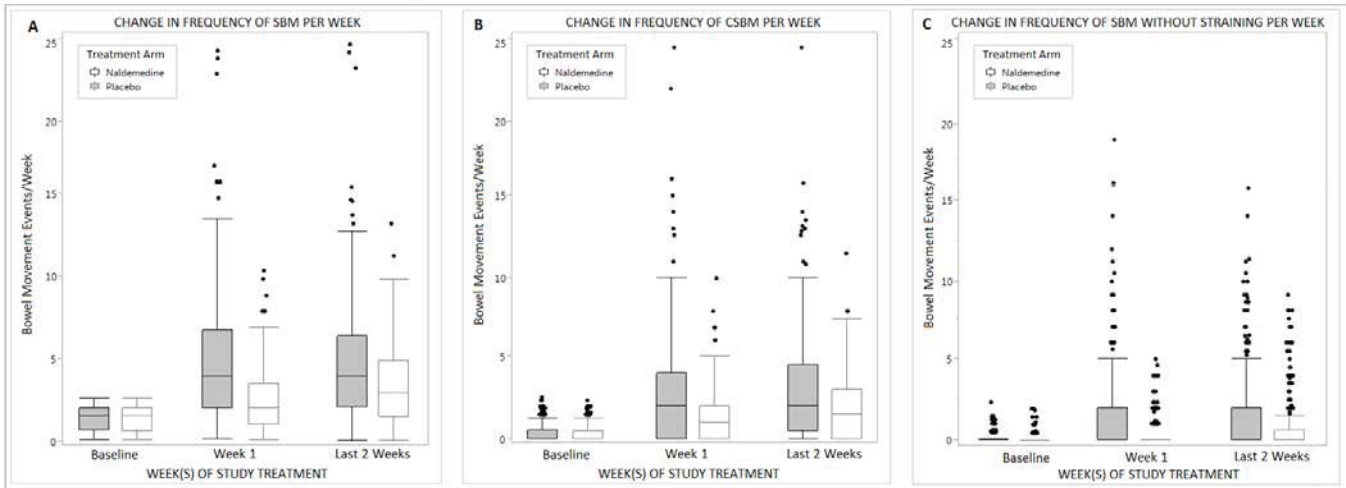
(Source: Reviewer's Table)

Abbreviations used in table: BM, bowel movement; CSBM, complete spontaneous bowel movement; CI, confidence interval; LS, least squares; SBM, spontaneous bowel movement; SE, standard error

Baseline frequencies per week for all three BM measures used for secondary analyses events (SBM, CSBM, and SBM without Straining) were similar between treatment arms. At baseline, frequency of CSBM and SBM without Straining per week were both lower than SBM frequency per week (0.39 and 0.09, respectively, vs. 1.31). Comparisons of frequencies per week for the 3 different BM events at baseline vs. the last 2 weeks if are shown graphically in Figure 9.

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Figure 8: Frequency of BM Events (SBM, CSBM, and SBM without Straining) at Baseline, Week 1 and the Last 2 Weeks of the Treatment Arm for the ITT Population of Study V9231



(Source: Reviewer's figure)

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Dose/Dose Response

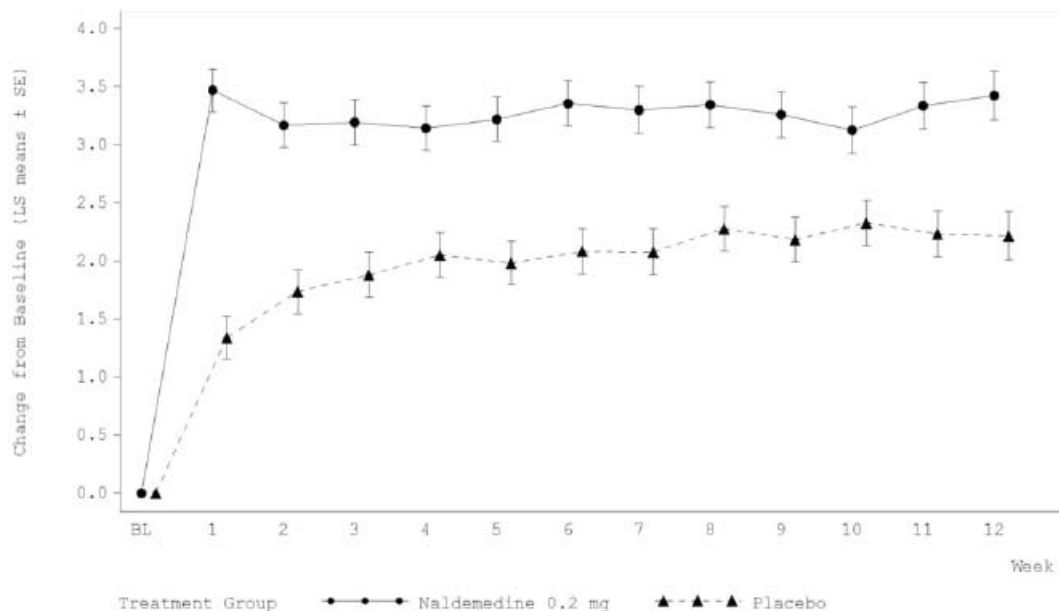
Only 1 naldemedine dosage (0.2 mg once daily) was evaluated in controlled phase 3 clinical trials, including Study V9231. Therefore, analyses of dose-response are limited to the phase 2 clinical trial (see Section 5.5.2).

Durability of Response

The responder definition for primary efficacy analyses includes a specific criterion (i.e., weekly response for 3 of the last 4 weeks of the treatment period) to incorporate a requirement for durability of treatment response as part of the overall definition of treatment response.

Demonstration of sustained treatment based on weekly response rates over time is shown in Figure 10.

Figure 9: Change in the Frequency of Spontaneous Bowel Movements per Week from Baseline to Each Week (Least-Squares Mean $\pm$ Standard Error) – Intent-to-Treat Population



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Baseline (BL) was 14 consecutive calendar day qualifying period during the Screening Period.

LS = least squares; SE = standard error.

(Source Applicant's Figure 11-1, Clinical Study Report: 1314V9231, page 90/1539)

Figure 9 (frequency of BM events at Baseline, Week 1, and the last 2 weeks of the treatment period) also illustrates the durability of naldemedine treatment effect.

Persistence of Effect

The half-life of naldemedine is relatively short, and there is no evidence to suggest that treatment effects would persist after stopping the drug.

Additional Analyses Conducted on the Individual Trial

Rescue Medication Use

During the screening period (i.e., baseline), mean ($\pm$ SD) frequency of rescue laxative use was 1.64 ($\pm$ 1.64) doses/week in the naldemedine group and 1.59 ($\pm$ 1.51) doses/week in the placebo group (range 0 to 7 doses for both groups).

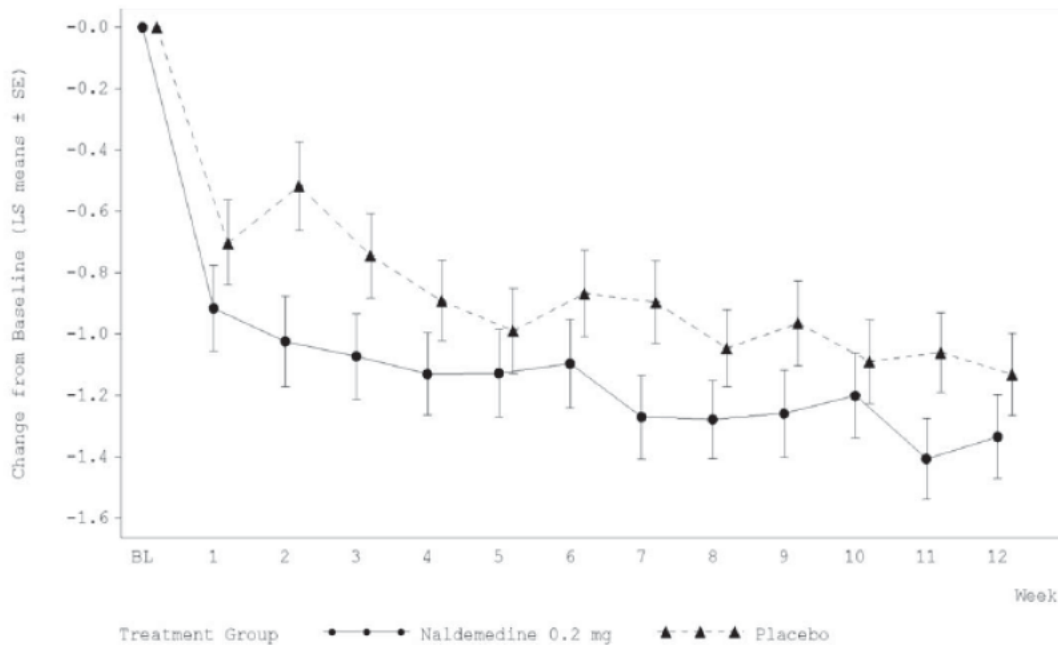
During the treatment period, 164 subjects (60.1%) in the naldemedine arm of the ITT population reported rescue medication use (≥ 1 dose), compared to 204 subjects in the placebo arm (75.0%). On the other hand, no rescue laxative use was reported in 86/238 subjects (36.1%) in naldemedine arm with ≥ 8 weeks of data vs. 63/246 subjects (25.6%) in the placebo

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group with ≥ 8 weeks of data.

A graph of the change in frequency of rescue laxative use per week from baseline (LS mean $\pm$ SE) to each study week by treatment arm is shown in Figure 11. Summary statistics of rescue laxative use at baseline, Week 1, and the last 2 weeks of the Treatment Period are shown in Table 41.

Figure 10: Change in the Frequency of Rescue Laxative Use per Week from Baseline (LS mean $\pm$ SE) in Study V92231, ITT Population



(Applicant's Figure 11-3, "Change in the Frequency of Rescue Laxative Use per Week from Baseline to Each Week (Least-Squares Mean $\pm$ Standard Error) – Intent-to-Treat Population

Abbreviations used in figure: ITT, intent-to-treat; LS, least squares; SE, standard error

Table 26: Frequency of Rescue Medication Use (Doses/Week) for the ITT Population of Study V9231

		Naldemedine (N=273)	Placebo (N=272)
Baseline (Screening Period)	Mean $\pm$ SD	1.64 $\pm$ 1.64	1.59 $\pm$ 1.51
	Median	1.17	1.5
	Min – Max	0 – 7	0 – 7
Entire Treatment Period	Mean $\pm$ SD	0.70 $\pm$ 1.42	0.88 $\pm$ 1.48
	Median	0	0
	Min – Max	0 – 7	0 – 7
Last 2 weeks of Treatment Period	Mean $\pm$ SD	0.59 $\pm$ 1.28	0.72 $\pm$ 1.37
	Median	0	0
	Min – Max	0 – 7	0 – 7

(Reviewer's table)

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Abbreviations used in table: Max, maximum; Min, minimum; SD, standard deviation

Subject Global Satisfaction (SGS) Scores

A Subject Global Satisfaction (SGS) evaluation was completed at Visit 7 (Week 12)/Early Termination, by 372 subjects in the ITT population (68.3%)—185 subjects in the naldemedine group (67.8%) and 187 subjects in the placebo group(68.8%). Results are shown in Table 26.

In the naldemedine group, 140 of the 185 subjects with completed assessments, 140/185 (75.7%) had scores 5-7 (i.e., markedly, moderately, or slightly improved), compared with 107/187 subjects (57.2%) in the placebo group (nominal p=0.0005).

By itself, SGS information is considered exploratory in nature. These data of subject satisfaction with treatment were proposed by the Clinical Outcomes Assessment (COA) team as a possible anchor score to assess the clinical meaningfulness of secondary endpoint data. At the request of the Agency, the Applicant created cumulative distribution function (CDF) plots of secondary endpoint data and SGS scores. These figures are located in the Appendix, Section 13.4; results are discussed in Section 7.1.3.

Table 27: Subject Global Satisfaction Scores for the ITT Population of Study V9231

SGS Score	Naldemedine (N=185)	Placebo (N=187)
Markedly Improved (7)	52 (28.1)	28 (15.0)
Moderately Improved (6)	39 (21.1)	41 (21.9)
Slightly Improved (5)	49 (26.5)	38 (20.3)
Unchanged (4)	27 (14.6)	58 (31.0)
Slightly Worsened (3)	4 (2.2)	7 (3.7)
Moderately Worsened (2)	11 (5.9)	8 (4.3)
Markedly Worsened (1)	3 (1.6)	7 (3.7)

(Source: Adapted from Table 14.2-3.13 in Section 14.2 of the Clinical Study Report: 1314V9231, page 700/1539)

Changes in Total and Free Testosterone in Males

The mean changes in total and free testosterone in males from baseline to Visit 7 (Week 12)/Early Termination for the naldemedine group were small and not meaningfully different from the placebo group.

6.2. Study V9232

6.2.1. Study Design

Overview and Objective

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The clinical trial design of Study V9232 was the same to Study V9231. Like Study V9231, Study V9232 was a 12-week, multicenter, international clinical trial entitled “A Randomized, Double-blind, Placebo-controlled, Parallel-group Study of Naldemedine in the Treatment of Opioid-induced Constipation in Subjects with Non-malignant Chronic Pain Receiving Opioid Therapy.” Refer to Section 6.1.1 for the description and discussion of the following clinical trial elements, which were the same to those reported for Study V9231:

- Overview and objective
- Trial design
- Study population (i.e., target enrollment, eligibility criteria)
- Study treatments and rescue medications
- Prohibited concomitant medications and non-medication study restrictions
- Study endpoints, including the primary endpoint and all secondary and exploratory endpoints
- Study procedures and assessments
- Statistical analysis plan, including efficacy analysis population

Study V9232 was conducted from 04 November 2013 (enrollment of the first subject) to 09 June 2015 (completion of the last subject).

Protocol Amendments

Two protocol amendments were applied to the original protocol for Study V9231, dated 04 October 2013 (concurrent with Amendment 1 of Study V9231), both of which were issued after initiation of enrollment on 29 August 2013.

- Amendment 1: 11 June 2014
- Amendment 2: 16 October 2014

The two protocol amendments for Study V9232 correspond with Amendments 2 and 3 for Study V9231, demonstrating consistency in the conduct of the 2 trials.

The key changes implemented with the V9232 protocol amendments included the following:

Amendment 1:

- Added clarification regarding discontinuation of regular use of laxatives at start of screening and through the 12-week Treatment Period
- Clarification regarding stratification based on morphine-equivalent dosing
- Clarification regarding allowable use of tramadol and tapentadol
- Clarification of exclusion criteria related to severe constipation prior to and during the Screening Period
- Clarification of primary efficacy endpoint related to last observation carried forward

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Amendment 2:

- Revised secondary efficacy endpoints to provide a more thorough clinical efficacy summary of naldemedine including effects from baseline to endpoint, baseline to the first week, straining, and CSBMs
- Added an exploratory endpoint to further assess the effect on SBMs without straining over time
- Removed PK assessment as an exploratory endpoint;
- Changed the mITT Population definition to produce a population that more accurately accounted for the challenges encountered by subjects required to use an EDC tool
- Modified the Safety Population definition to be more inclusive in order to obtain a larger population
- Further clarified the definition of insufficient primary endpoint data and “nonresponse” week

6.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant reported that operating procedures and audit programs were by the CRO and Applicant in accordance with the Good Clinical Practice (GCP) guidelines, as documented by the International Conference on Harmonization (ICH) and the FDA.

Financial Disclosure

None of the site investigators who participated in this clinical trial had disclosable financial information. Additional details are provided in Section 13.2.

Subject Disposition

The subject disposition for all screened subjects in V9232 is shown in Figure 12. Of the 277 subjects randomized to naldemedine, 5 subjects were not dosed (vs. 0 in the placebo arm).

- Subject 22309-001- randomized accidentally by the site (ineligible due to) and was discontinued before receiving the first dose of study drug,
- Subject 22316-016 was randomized but not dosed due to ineligibility because the patient was unable to comply with all study procedures

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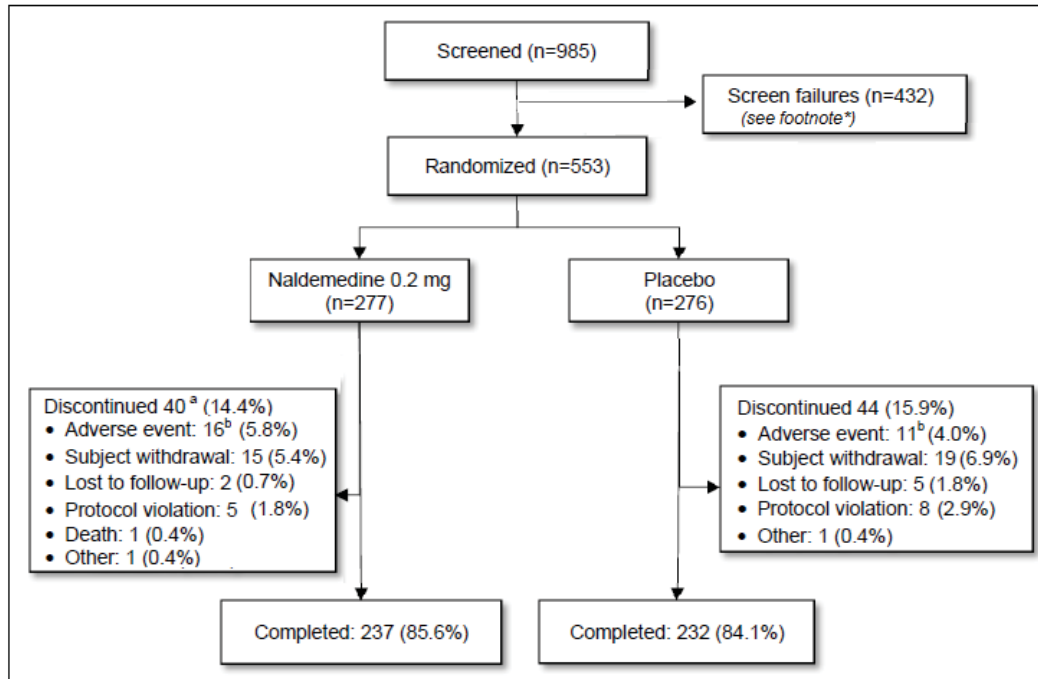
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- Subject 22324-002 withdrew consent prior to the first dose of study drug as the subject could not stay at the site for the time required to complete all study procedures required for the randomization visit
- Subject 22335-018 withdrew consent prior to dosing due to “personal reasons”
- Subject 22351-008 was randomized prematurely, and prior to dosing, was found to have a mildly tender lump in the abdomen, which, according to the Investigator, required further evaluation. The subject was discontinued prior to the first dose of study drug

As shown in Figure 13, the study completion and discontinuation rates were similar between treatment groups in Study V9232. Forty (14.4%) in the naldemedine group and 44 (15.9%) in the placebo group discontinued study participation, and the reasons for discontinuation were also generally similar between groups. Sixteen subjects (5.8%) in the naldemedine arm vs 11 subjects (4.0%) in the placebo arm in the placebo arm withdrew due to a TEAE, including 2 subjects in each treatment group for whom the onset of the TEAE occurred prior to the first dose of study medication. This difference in TEAE-related discontinuation rates between V9232 treatment arms (31% difference) is notably less than Study V9231, in which study discontinuations due to TEAEs were almost 3-fold higher in the naldemedine arm as compared to the placebo arm. (Discontinuations due to TEAEs are discussed in detail in the Safety Evaluation in Section 8.)

Overall, a similar proportion of subjects (naldemedine 85.6%; placebo 84.1%) in both treatment groups completed the study.

Figure 11: Subject Disposition for Study V9232



(Source: Adapted from Applicant's Table 10-1, "Consort Diagram for Subject Disposition - All Subjects Enrolled", page 63/1630, Clinical Study Report: 1315V9232; NDA 208854, Module 5.3.5.1)

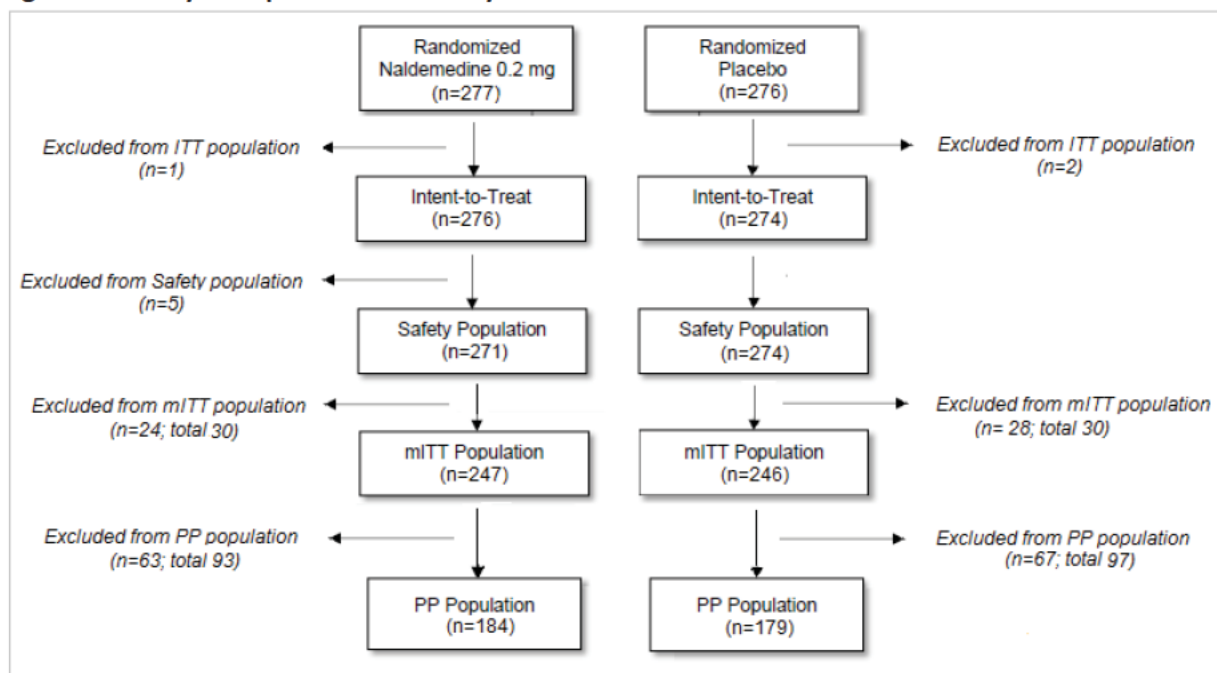
^a Includes 5 subjects who were randomized but not dosed

^b Includes 2 subjects discontinued due to an adverse event with an onset prior to study drug initiation

***Reasons for screen failure: (n=432)**

- eDiary eligibility (n=120)
- eDiary compliance (n=41)
- Positive urine drug screen (n=19)
- Screening laboratory tests (n=2)
- Medical history (n=36)
- Unstable laxative/opioid regimen (n=32)
- Prohibited concomitant medication (n=4)
- Laboratory results (n=52)
- Other (n=126)

Figure 12: Analysis Populations for Study V9232



(Source: Reviewer’s figure, adapted from Applicant’s Figure 10-2, “Consort Diagram for Analysis Populations – All Randomized Subjects” Clinical Study Report: 1315V9232, page 67/1630)

Table 28: Randomized Subjects Excluded from Analysis Populations in Study V9232 (N=553)

Analysis Population [†]	Reason for Exclusion [#]	Treatment Arm (n, (%))	
		Naldemedine (N=277)	Placebo (N=276)
ITT	Double enrollment at different study sites	1 (0.4)	2 (0.7)
Safety	No study drug administered	5 (1.8)	0
mITT	Did not complete first 4 weeks of the study with at least 4 days of diary entries	29 (10.5)	28 (10.1)
PP	Any PP *		
	Withdrawal before Day 81 of the study treatment period	37 (13.4)	42 (15.2)
	Use of rescue medication <60 hours after BM	26 (9.4)	27 (9.8)
	Prohibited concomitant medications/therapy	21 (7.6)	26 (9.4)
	Compliance <80% or >120%	23 (8.3)	20 (7.2)
	Evidence of active medical diseases affecting bowel transit*	2 (0.7)	3 (1.1)
	<30 mg average TDD of opioid medication during treatment period	2 (0.7)	2 (0.7)
	Positive serologic test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), or active hepatitis A virus (HAV)	1 (0.4)	3 (1.1)

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Analysis Population [†]	Reason for Exclusion [#]	Treatment Arm (n, (%))	
		Naldemedine (N=277)	Placebo (N=276)
	Evidence of significant structural GI abnormalities or history of bowel surgery**	1 (0.4)	1 (0.4)
Total		148	154

(Source: Reviewer's based on Applicant's Figure 10-1, "Consort Diagram for Subject Disposition – All Subjects Enrolled", Clinical Study Report: 1315V9232, page 65/1630; Analysis datasets, NDA 208854, Module 5.3.5.1)

Abbreviations used in table: BM, bowel movement; IMP, investigational medicinal product; ITT, intent-to-treat; mg, milligrams; mITT, modified intent-to-treat; PP, per protocol; TDD, total daily dose

*Excluded subjects may have had ≥1 protocol deviation resulting in exclusion

** i.e., ileus, uncontrolled hypothyroidism, irritable bowel syndrome (IBS), inflammatory bowel disease, fecal incontinence

Protocol Violations/Deviations

A total of 302 major protocol deviations were reported for randomized subjects in Study V9232—148 in the naldemedine group and 154 the placebo group—and are summarized in Table 27 and Table 28.

At least 1 major protocol deviation was reported for 220 subjects (103 subjects in the naldemedine group and 117 subjects in the placebo group). Unlike Study V9232, the percentage of subjects without the minimum required efficacy data for inclusion in both the mITT and PP populations were similar between groups. The most commonly reported protocol deviation was subject withdrawal before Day 81 of the Treatment Period: 37 (13.4%) subjects in the naldemedine group and 42 (15.2%) subjects in the placebo group.

Table 29: Major Protocol Deviations in Randomized Subjects, Study V9232

Protocol Deviation Category	Naldemedine (N=277)	Placebo (N=276)
Any	103 (37.2)	117(42.4)
Treatment deviation	51 (18.4)	55 (19.9)
Inappropriate rescue medication use	26 (9.4)	27 (9.8)
Prohibited concomitant medication	21 (7.6)	26 (9.4)
Exclusion Criteria	4 (1.4)	7 (2.5)
Enrollment error	1 (0.4)	2 (0.7)

(Source: Reviewer's table based on analysis datasets, NDA 208854, Module 5.3.5.1)

Demographic and Baseline Characteristics

Overall, the treatment arms in Study V9232 were well-balanced with respect to demographics, prior medical history, and concomitant medical conditions and treatments. Baseline disease-related characteristics were also similar between groups.

Subject Demographics

Subject demographics for the ITT population for Study V9232 are summarized in Table 29, with a breakdown of the ITT population and clinical sites by country of origin shown, along with Study V9231 data, in Section 7.1.2 (Table 14). The Study V9232 study population had a similar imbalance in age distribution between treatment arms as Study V9231, with a higher proportion of subjects between ages 40 and 65 years old. In addition, both treatment arms in Study V9232 had small numbers of subjects aged ≥ 75 years old (9 subjects in the naldemedine group and 5 subjects in the placebo group).

Also similar to Study V9231, mean and median body mass index (BMI) of the V9232 study population were in the obese range (31.3 kg/m^2 and 30.3 kg/m^2 , respectively), and $>50\%$ of study subjects had a BMI in the obese range. Average BMI values were similar between treatment arms, although there were fewer subjects in the naldemedine arm with BMI in the normal range compared to placebo (16.3% vs. 19.3%, respectively) and more subjects in the overweight range (30.4% vs. 26.6%, respectively). The high prevalence of obesity in this population is reflective of the high overall morbidity of this patient population and is likely a good representation of the post-marketing treatment population.

Of the clinical trials sites who participated in Study V9232, $>75\%$ were in the United States, and enrollment at these sites accounted for 87% of the subjects in the V9232 ITT population.

Table 30: Demographics for Subjects in Study V9232, ITT Population (N=550)

Demographic Parameter		Naldemedine (N=276)	Placebo (N=274)	Total (N=550)
Age (years)	Mean $\pm$ SD	54.1 $\pm$ 10.5	52.9 $\pm$ 11.4	53.5 $\pm$ 11.0
	Median	54.0	54.0	54.0
	Range	25 – 79	19 – 79	19 – 79
Age Category (years), n (%)	<40	22 (8.0)	40 (14.6)	62 (11.3)
	≥ 40 to <65	210 (76.1)	196 (71.5)	406 (73.8)
	≥ 65	44 (15.9)	38 (13.9)	82 (14.9)
	≥ 75	9 (3.3)	5 (1.8)	14 (2.5)
Sex, n (%)	Male	111 (40.2)	106 (38.7)	217 (39.5)
	Female	165 (59.8)	168 (61.3)	333 (60.5)
Height (cm)	n	275	272	547
	Mean $\pm$ SD	168.7 $\pm$ 10.5	168.6 $\pm$ 9.6	168.61 $\pm$ 10.0
	Median	168.0	167.6	167.7
	Range	135.9 – 200.7	142.0 – 192.0	135.9 – 200.7
Body Weight (kg)	n	276	273	549
	Mean $\pm$ SD	89.2 $\pm$ 21.2	89.07 $\pm$ 22.2	89.15 $\pm$ 21.7
	Median	87.0	86.1	86.6
	Range	43.6 – 173.4	41.0 – 163.8	41.0 – 173.4

Demographic Parameter		Naldemedine (N=276)	Placebo (N=274)	Total (N=550)
BMI (kg/m ²)	n	275	272	547
	Mean ± SD	31.4 ± 7.0	31.3 ± 7.5	31.3 ± 7.3
	Median	30.2	30.3	30.3
	Range	18.4 – 59.5	17.9 – 58.9	17.9 – 59.5
BMI Category (kg/m ²), n (%)	<18.5	1 (0.4)	3 (1.1)	4 (0.7)
	>=18.5 to <25.0	45 (16.3)	53 (19.3)	98 (17.8)
	>=25.0 to <30.0	84 (30.4)	73 (26.6)	157 (28.5)
	>=30.0	145 (52.5)	143 (52.2)	288 (52.4)
	Missing	1 (0.4)	2 (0.7)	3 (0.5)
Race, n (%)	American Indian or Alaska Native	3 (1.1)	4 (1.5)	7 (1.3)
	Asian	2 (0.7)	3 (1.1)	5 (0.9)
	Black	49 (17.8)	39 (14.2)	88 (16.0)
	Native Hawaiian/ Other Pacific Islander	0	1 (0.4)	1 (0.2)
	White	222 (80.4)	227 (82.8)	449 (81.6)
Ethnicity, n (%)	Hispanic/Latino	26 (9.4)	27 (9.9)	53 (9.6)
	Not Hispanic/Latino	250 (90.6)	247 (90.1)	497 (90.4)

(Source: Reviewer’s table adapted from Applicant’s Table 2, “Demographic and Baseline Characteristics – Intent-to-Treat Population”, Clinical Study Report: 1315V9232, pages 69-72/1630)

Abbreviations used in table: %, percentage; BMI, body mass index; cm, centimeter; ITT, intent-to-treat; kg, kilogram; m², square meters; n, number of subjects; SD, standard deviation

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

• **Baseline SBM Frequency**

Mean frequency of SBMs at baseline for both treatment arms of the V9232 ITT population was 1.2 SBM/week (range 0 to 2.5 SBM/week). Both groups also had similar distribution of baseline SBM frequency (Table 30). No subjects had a weekly SBM frequency of ≥3 SBM/week, consistent with the eligibility criteria used to establish a diagnosis of OIC. The severity of other baseline constipation-related characteristics and symptoms were also similar between groups.

Table 31: Baseline Weekly Frequency of Spontaneous Bowel Movements in the ITT Population, Study V9232 (N=550)

SBM Frequency		Naldemedine 0.2 mg (N=276)	Placebo (N=274)	Total (N=550)
Summary Statistics (SBM/week)	Mean ± SD	1.2 ± 0.8	1.2 ± 0.7	1.2 ± 0.7
	Median	1.1	1.1	1.1
	Range	0 – 2.5	0 – 2.5	0 – 2.5

SBM Frequency		Naldemedine 0.2 mg (N=276)	Placebo (N=274)	Total (N=550)
Categories (SBM/week) n (%)	<1	88 (31.9)	87 (31.8)	175 (31.8)
	>=1 to <2	115 (41.7)	114 (41.6)	229 (41.6)
	>=2 to <3	73 (26.4)	73 (26.6)	146 (26.5)
	>=3	0	0	0

(Source: Adapted from Applicant's Table 10-3, "Spontaneous Bowel Movements per Week at Baseline – Intent-to-Treat Population", Clinical Study Report: 1314V9231, page 71/1539)

Abbreviations used in table: ITT, intent-to-treat; n, number; SBM, spontaneous bowel movement

- **Baseline Opioid Use**

Baseline opioid use for the ITT population of Study V9232 was assessed during the 14-day Screening Period. For each subject, a baseline mean total daily dose (TDD) of opioids was calculated and expressed in morphine equivalents based on standard conversion factors. Baseline opioid TDD data are shown in Table 16.

Similar to Study V9231, the mean TDD of opioid was higher for the placebo group than the naldemedine group, though the difference was more modest (<6%). Also consistent with Study V9231, the median dose was the same for both groups.

In Study V9232, only 3 subjects (1 naldemedine, 2 placebo) had mean TDD below the minimum required dose of 30 mg morphine equivalents/day.

Table 32: Baseline Total Daily Dosage (TDD) of Opioid Medication (mg Morphine Equivalents) in the ITT Population, Study V923321 (N=550)

Opioid TTD (Morphine Equivalents)		Naldemedine (N=276)	Placebo (N=274)	Total (N=550)
Dose (mg)	Mean ± SD	118.0 ± 122.0	123.9 ± 146.1	120.9 ± 134.5
	Median	77.5	75.0	75.0
	Range	29.0 – 900.0	0 – 1440.0	0 – 1440.0
	Q1 – Q3	40.0 – 150.0	40.0 – 150.0	40.0 – 150.0
Dose Ranges (mg), n (%)	<30	1 (0.4)	2 (0.7)	3 (0.5)
	>=30 to <=100	164 (59.4)	164 (59.9)	328 (59.6)
	>100 to <=200	71 (25.7)	63 (23.0)	134 (24.4)
	>200 to <=400	29 (10.5)	34 (12.4)	63 (11.5)
	>400	11 (4.0)	11 (4.0)	22 (4.0)

(Source: Adapted from Applicant's Table 10-4, "Average Total Daily Dose of Opioid at Baseline: Electronic Data Capture Data – Intent-to-Treat Population", Clinical Study Report: 1315V9232, page 74/1539)

Abbreviations used in table: %, percentage; ITT, intent-to-treat; mg, milligrams; Max, maximum; Min, minimum; n, number of subjects; Q1, quartile 1; Q2, quartile 2; SD, standard deviation; TDD, total daily dose

- **Opioid medications**

The specific opioid medications used by subjects in Study V9232 are shown in Table 32 (frequency of use). Opioid medications were generally similar between arms. For both arms, oxycodone commonly used opioid. Use of tramadol and tapentadol (analgesics with dual mechanisms of action, considered weak opioids) was greater in the placebo arm (9.5%, vs. 6.5% in the naldemedine arm).

Table 33: Opioid Medications Used in the ITT Population of Study V9232

	Naldemedine (N=276)	Placebo (N=274)
Oxycodone	127 (46.0)	136 (49.6)
Hydrocodone	89 (32.2)	93 (33.9)
Morphine	62 (22.5)	61 (22.3)
Fentanyl	35 (12.7)	34 (12.4)
Tramadol	15 (5.4)	20 (7.3)
Hydromorphone	23 (8.3)	12 (4.4)
Oxymorphone	11 (4.0)	8 (2.9)
Tapentadol	3 (1.1)	6 (2.2)
Dihydrocodeine	0	3 (1.1)
Meperidine	1 (0.4)	1 (0.4)
Codeine	0	1 (0.4)
Buprenorphine	1 (0.4)	0

(Source: Reviewer's table)

- **Other Concomitant Medications**

Non-opioid analgesics

In addition to opioids, 151 subjects in the naldemedine group (55%) and 170 subjects in the placebo group (65%) were receiving ≥ 1 non-opioid pain medication (Table 33). The most classes of non-opioid analgesics in both groups were NSAIDs and GABA analogues, such as gabapentin, pregabalin, and gabapentin. NSAID use was similar between treatment arms in Study V9232, but use of GABA analogues higher in the placebo group (38.3%, vs. 29.7% in the naldemedine arm).

Table 34: Non-Opioid Analgesics Used by Subjects in the ITT Population of Study V9232

	Naldemedine (N=276)	Placebo (N=274)
Non-steroidal anti-inflammatory drugs	111 (40.2)	113 (41.2)
GABA analogues (e.g., gabapentin, pregabalin, topiramate)	82 (29.7)	105 (38.3)
Anilides (e.g., acetaminophen)	28 (10.1)	23 (8.3)
Selective serotonin (5-HT ₁) agonists (i.e., triptans)	13 (.7)	16 (5.8)
COX-2 Inhibitors	4 (1.4)	8 (2.9)
Salicylic acid derivatives	1 (0.4)	2 (0.7)

(Source: Reviewer's table based on analysis data, NDA 208854, Module 5.3.5.1)

Abbreviations used in table: COX, cyclooxygenase; GABA, gamma-aminobutyric acid

Concomitant Medications (Excluding Analgesics and Laxatives)

Classes of medications used by $\geq 5\%$ of the ITT population in Study V9232 are shown in Table 34. Concomitant medication use was generally similar between groups. Centrally acting muscle relaxants comprised the most common class of concomitant medications (excluding analgesics and laxatives) in both treatment arms ($>1/3$ of subjects in each arm). Other potentially constipating medications with higher rate in the placebo arm are multivitamins

This reviewer has identified some differences between groups, notably use of both serotonin-norepinephrine reuptake inhibitors (SNRIs) and SSRIs, antidepressants with common side effect of constipation, were both lower in the naldemedine arm, with rates 13.4% and 17.4% in the naldemedine arm vs. 19.0% and 20.4% in the placebo arm, for SNRIs and SSRIs, respectively. Use of thyroid hormone was higher in the placebo group and is a reflection of the higher rate of hypothyroidism among those subjects. On the hand, rates of use for beta-blockers, alpha-blockers, and sedative-hypnotic sleep agents (e.g., zolpidem, zaleplon, eszopiclone, etc.), other medications associated with constipation, were higher in the naldemedine arm.

Table 35: Classes of Medications with Reported Use in $\geq 5\%$ of the ITT Population of Study V9232

	Naldemedine (N=276)	Placebo (N=274)
Muscle Relaxants, Centrally Acting	95 (34.4)	94 (34.3)
Benzodiazepines	77 (27.9)	92 (33.6)
Proton Pump Inhibitors	82 (29.7)	84 (30.7)
HMG CoA Reductase Inhibitors	79 (28.6)	74 (27.0)
ACE Inhibitors	64 (23.2)	63 (23.0)
Beta Blockers	61 (22.1)	46 (16.8)
Selective Serotonin Reuptake Inhibitors	48 (17.4)	56 (20.4)
Serotonin–Norepinephrine Reuptake Inhibitors	37 (13.4)	52 (19.0)
Platelet Aggregation Inhibitors (Excl. Heparin)	48 (17.4)	42 (15.3)
Inhaled Beta-2-Adrenoreceptor Agonists	48 (17.4)	42 (15.3)
Calcium Channel Blockers	44 (15.9)	44 (16.0)
Thyroid Hormones	34 (12.3)	51 (18.6)
Systemic Antibiotics, Oral	37 (13.4)	40 (14.6)
Sedative Hypnotic Sleep Agents	42 (15.2)	29 (10.5)
Blood Glucose Lowering Drugs (except Insulin)	36 (13.0)	35 (12.8)
Systemic Antihistamines	35 (12.7)	34 (12.4)
Thiazides	35 (12.7)	34 (12.4)
Vitamin D And Analogues	30 (10.9)	35 (12.8)
Monoamine Reuptake Inhibitors	28 (10.1)	29 (10.5)
Other Antidepressants (Trazodone and Remeron)	27 (9.8)	30 (10.9)
Multivitamins	23 (8.3)	34 (12.4)
Inhaled Corticosteroids	26 (9.4)	25 (9.1)

	Naldemedine (N=276)	Placebo (N=274)
Angiotensin II Antagonists	26 (9.4)	25 (9.1)
Loop Diuretics	20 (7.2)	25 (9.1)
Bupropion	19 (6.9)	21 (7.7)
Systemic Corticosteroids	16 (5.8)	24 (8.8)
Vitamin B12	19 (6.9)	18 (6.6)
Intranasal Corticosteroids	16 (5.8)	21 (7.7)
Potassium Supplements	11 (4.0)	19 (6.9)
Insulin	15 (5.4)	14 (5.1)
Triptans (Selective Serotonin Agonists)	13 (4.7)	16 (5.8)
Alpha Adrenergic Antagonists	19 (6.9)	8 (3.3)
Fish Oil/Omega Fatty Acids	9 (3.3)	18 (6.6)
Psychostimulants/Centrally Acting Sympathomimetics	9 (3.3)	17 (6.2)

(Source: Reviewer's Table)

- Concomitant medical conditions and medical history

Medical History: Causes of non-cancer pain

Table 35 lists the underlying etiology of non-cancer pain reported in >2% of the ITT population in Study V9232. By far, the most common source of pain was back pain, reported by 64.1 and 59.9% of subjects in the naldemedine and placebo arms, respectively. Overall, the types of pain reported by subjects were similar between treatment arms.

Table 36: Causes of Non-Cancer Pain in >2% of the ITT population in Study V9232

	Naldemedine (N=276)	Placebo (N=274)	Total (N=550)
Back Pain	153 (55.4)	142 (51.8)	295 (53.6)
Pain	30 (10.9)	26 (9.5)	56 (10.2)
Arthralgia	21 (7.6)	22 (8.0)	43 (7.8)
Neck Pain	19 (6.8)	22 (8.0)	41 (7.5)
Osteoarthritis	16 (5.8)	22 (8.0)	38 (6.9)
Intervertebral Disc Compression/Degeneration	16 (5.8)	16 (5.8)	32 (5.8)
Intervertebral Disc Displacement/Protrusion	16 (5.8)	11 (4.1)	27 (4.9)
Fibromyalgia	10 (3.6)	12 (4.4)	22 (4.0)
Musculoskeletal Pain	9 (3.2)	10 (3.6)	19 (3.5)
Pain In Extremity	6 (2.2)	8 (2.9)	14 (2.5)
Rheumatoid Arthritis	5 (1.8)	9 (3.2)	14 (2.5)
Spinal Osteoarthritis/Spondylolysis	6 (2.2)	7 (2.5)	13 (2.4)
Post Laminectomy Syndrome	7 (2.5)	5 (1.8)	12 (2.2)
Radicular Pain/Radiculopathy	6 (2.2)	5 (1.8)	11 (2.0)
Spinal Stenosis	2 (0.7)	8 (2.9)	10 (1.8)
Neuropathy Peripheral	5 (1.8)	5 (1.8)	10 (1.8)

Medical History: General

The most common medical conditions among subjects in Study V9232, occurring in >1/3 of ITT population of both treatment arms, were back pain (also the most commonly reported cause of subjects' non-cancer pain), hypertension, depression, dyslipidemia, anxiety, and insomnia. These results are similar to Study V9231. All medical conditions reported in at least 10% of the ITT population are listed in Table 36.

Of note, GERD was more common in the placebo arm (relevant for abdominal pain assessments), as well as hypothyroidism, which is strongly associated with constipation but should not have been a confounding factor because thyroid control was a prerequisite for study for study participation. In the placebo arm, anxiety and depression were also more common than in the naldemedine, which is consistent with the higher rate of SSRI and SNRI use in that treatment arm.

In the naldemedine arm, the prevalence of hypertension was higher than the placebo arm. This is an important consideration for interpretation of hypertension-related TEAEs, particularly because there is a plausible mechanism for elevated blood pressure with naldemedine and other PAMORAs.

Table 37: Medical Conditions Reported in >10% of Subjects in the ITT Population, Study V9232

	Naldemedine (N=276)	Placebo (N=274)	Overall (N=550)
Back Pain	181 (65.6)	170 (62.0)	351 (63.8)
Hypertension	148 (53.6)	124 (45.3)	272 (49.5)
Depression	114 (41.3)	134 (48.9)	248 (45.1)
Dyslipidemia	121 (43.8)	112 (40.9)	233 (42.4)
Anxiety/Anxiety Disorder	85 (30.8)	107 (39.1)	192 (34.9)
Insomnia	97 (35.1)	94 (34.3)	191 (34.7)
Osteoarthritis	77 (27.9)	86 (31.4)	163 (29.6)
Gastroesophageal Reflux Disease	74 (26.8)	88 (32.1)	162 (29.5)
Headache/Migraine	66 (23.9)	83 (30.3)	149 (27.1)
Drug Hypersensitivity	67 (24.3)	78 (28.5)	145 (26.4)
Hysterectomy	60 (21.7)	75 (27.4)	135 (24.5)
Intervertebral Disc Displacement/Protrusion	56 (20.3)	71 (25.9)	127 (23.1)
Muscle Spasms	60 (21.7)	65 (23.7)	125 (22.7)
Arthralgia	55 (19.9)	65 (23.7)	120 (21.8)
Menopause/Postmenopause	59 (21.4)	60 (21.9)	119 (21.6)
Intervertebral Disc Compression/Degeneration	55 (19.9)	54 (19.7)	109 (19.8)
Diabetes Mellitus	49 (17.8)	48 (17.5)	97 (17.6)
Spinal Fusion/Surgery	46 (16.7)	41 (15.0)	87 (15.8)
Seasonal Allergy	41 (14.9)	46 (16.8)	87 (15.8)
Asthma/Bronchospasm	42 (15.2)	44 (16.1)	86 (15.6)

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	Naldemedine (N=276)	Placebo (N=274)	Overall (N=550)
Spinal Osteoarthritis/Spondylolysis	36 (13.0)	50 (18.2)	86 (15.6)
Neck Pain	39 (14.1)	44 (16.1)	83 (15.1)
Pain (Not Otherwise Specified)	39 (14.1)	40 (14.6)	79 (14.4)
Hypothyroidism	34 (12.3)	43 (15.7)	77 (14.0)
Peripheral Neuropathy	38 (13.8)	37 (13.5)	75 (13.6)
Cholecystectomy	36 (13.0)	33 (12.0)	69 (12.5)
Tubal ligation	46 (16.7)	23 (8.4)	69 (12.5)
Fibromyalgia	29 (10.5)	38 (13.9)	67 (12.2)
Obesity	35 (12.7)	29 (10.6)	64 (11.6)
Appendectomy/Appendicitis	29 (10.5)	31 (11.3)	60 (10.9)
Radicular Pain/Radiculopathy	31 (11.2)	28 (10.2)	59 (10.7)
Arthritis/Arthropathy	28 (10.1)	31 (11.3)	59 (10.7)
Arthroplasty/Joint Surgery	23 (8.3)	36 (13.1)	59 (10.7)
Intervertebral Disc Operation	28 (10.1)	28 (10.2)	56 (10.2)

(Source: Reviewer's table)

Study Compliance

- Treatment Compliance- Study Drug

Study drug compliance rates were similar between treatment groups. Mean compliance with study drug during the Treatment Period was 95.86% for the naldemedine group and 96.42% for the placebo group.

- Treatment Compliance- Study Drug Diary completion

Seventy-eight subjects had ≥ 1 week with non-evaluable efficacy data (i.e., data for < 4 of 7 days)—36 in the naldemedine group and 42 in the placebo group. Only 2 active subjects (both in the naldemedine group) had non-evaluable data for ≥ 3 study weeks, suggesting overall good eDiary compliance during study participation.

Efficacy Results – Primary Endpoint

Proportion of Spontaneous Bowel Movement (SBM) Responders

Responder definitions in Study V9232 were the same as those used in Study V9231 (See Section 6.1.2).

The proportion of responders by treatment group and the between-group comparisons for the ITT Population are summarized in Table 37. The proportion of SBM responders in the naldemedine group was 52.5% vs. 33.6% in the placebo group (+18.9%, $p < 0.0001$), a statistically

significant difference between the 2 groups. Similar to study V9231, these results are statistically significant, and these results are even more robust than those from Study V9231.

Table 38: Primary Efficacy Analysis: Difference in Proportion of Responders, Study V9231 (ITT Population)

		Naldemedine (N=276)	Placebo (N=274)
Proportion of Responders	% (n/N)	52.5 (145/276)	33.6 (92/274)
	95% CI (%)	46.5, 58.6	28.0, 39.5
Comparison between arms	Difference of Proportions (%)	18.9	
	95% CI (%)	10.8, 27.0	
	p-value	<0.0001	

(Source: Adapted from Applicant's Table 11-1, "Proportion of Responders: Primary Analysis – Intent-to-Treat Population", Clinical Study Report: 1315V9232, page 79/1630)

Table 39: Difference in Proportion of Responders by Opioid Dose Strata, Study V9232, ITT Population

Opioid Dose strata (mg*)	Treatment Arm, % (n/N)		Difference of Proportions (Naldemedine-Placebo, %)
	Naldemedine (N=273)	Placebo (N=272)	
30-100	49.0 (75/155)	35.9 (55/153)	13.1
>100	45.8 (54/118)	32.8 (39/119)	13.0

(Source: Adapted from Applicant's Table 11-2, "Proportion of Responders: Primary Analysis – Intent-to-Treat Population", Clinical Study Report: 1315V9232, page 81/1630)

Results for all 6 primary endpoint sensitivity analyses were consistent with the primary (ITT population) analysis of the primary endpoint. In each case, the proportion of responders in the naldemedine group was higher than in the placebo group with statistically significant differences between groups (p-value range <0.0001 to 0.0007, where the highest p-value is for the "Worst Case" analysis.) These results support that pre-specified definitions for evaluable data and methods for handling missing data did not significantly impact the interpretability/reliability of primary endpoint data.

Of the 6 sensitivity analyses, the "modified worst case" analysis is the one that best addresses the risk of bias due to correction of weekly BM event frequencies (i.e., adjustment based on the number of completed diary entries for the week). As shown in Table 39, the modified worst case analysis of primary endpoint data yielded very similar results to the primary (ITT population) analysis. With use of uncorrected SBM frequencies for the modified worst case analysis, the responder classification for only 1 of the 545 subjects in the ITT population differed from the primary analysis classification.

As predicted by the similar exclusion rate for the mITT population, the treatment effect was not substantially higher for the mITT population, compared to the primary analysis, as was observed for Study V9231. Although TEAE-related discontinuations still occurred relatively

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early during the treatment period, the overall dropout rate during the 1st 4 weeks was more similar in this study. However, as expected, the individual group response rates are highest among the mITT and PP populations for Study V9232.

Table 40: Sensitivity Analyses for the Primary Efficacy Endpoint, Study V9232

Sensitivity Analysis	Parameter	Treatment Arm		Difference of Proportions	
		Naldemedine (N=276)	Placebo (N=274)	Nald-Placebo, % 95% CI	p-value
Primary Analysis (ITT) (N=550)	N	276	274	18.9 (10.8, 27.0)	<0.0001
	n	145	92		
	%	52.5	33.6		
Observed Case (N=550)	N	276	274	19.0 (10.8, 27.0)	<0.0001
	n	146	92		
	%	52.9	33.9		
Complete Case (N=434)	N	219	214	20.5 (11.5, 29.9)	<0.0001
	n	135	88		
	%	61.6	41.1		
Worst Case (N=545)	N	276	274	13.9 (5.9, 21.8)	0.0007
	n	121	82		
	%	43.8	29.9		
Modified Worst Case (N=550)	N	276	274	19.3 (11.2, 27.4)	<0.0001
	n	145	91		
	%	52.5	33.2		
mITT (N=493)	N	247	246	20.3 (11.7, 28.9)	<0.0001
	n	141	90		
	%	57.1	36.6		
Per Protocol (N=363)	N	184	179	19.5 (9.8, 29.9)	0.0001
	n	113	75		
	%	61.4	41.9		

(Source: Reviewer's Table)

Data Quality and Integrity – Reviewers' Assessment

Similar discrepancies were identified in opioid dose data of Study V9232 as Study V9231. Refer to Section 7.1.2 for discussion of these data integrity concerns and their potential impact on the interpretation of study data.

Efficacy Results – Secondary endpoints

The same 4 secondary endpoints were pre-specified for both Study V9231 and Study V9232:

1. Change in the frequency of spontaneous bowel movements per week from baseline to the last 2 weeks of the treatment period

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2. Change in the frequency of spontaneous bowel movements per week from baseline to week 1 of the treatment period
3. Change in the frequency of complete spontaneous bowel movements (CSBM) per week from baseline to the last 2 weeks of the treatment period
4. Change in the Frequency of Spontaneous Bowel Movements without Straining per Week from Baseline to the Last 2 Weeks of the Treatment Period

The ITT population was the primary analysis population used for secondary endpoint analyses.

Like Study V9231, treatment differences between the naldemedine and placebo arms were statistically significant for all 4 key secondary endpoints (p-values <0.0001 to 0.0011), i.e., the naldemedine group had statistically greater increases in frequency of SBM per week from baseline to the last 2 weeks of the treatment period, SBM per week from baseline to Week 1 of treatment, CSBM per week from baseline to the last 2 weeks of the treatment period, and SBM without straining per week from baseline to the last 2 weeks of the treatment period, compared to the placebo group.

As pre-specified in the statistical analysis plan, the frequencies of BM events per week used for secondary endpoint analyses were adjusted based on the number of diary entries completed for the particular week. However, this methodology raises concern for potential responder bias. Therefore, the Applicant conducted post-hoc analyses using unadjusted BM frequencies (i.e., only observed BM events per week) at Agency's request. A comparison of results from adjusted and unadjusted data are shown in

Statistically, these re-analyses were consistent with the original analyses (p-values <0.0001 to 0.0014), thus demonstrating the overall robustness of these secondary efficacy data. However, treatment differences between groups were consistently smaller using unadjusted data compared to analyses with adjusted data, albeit less than those observed in Study V9231.

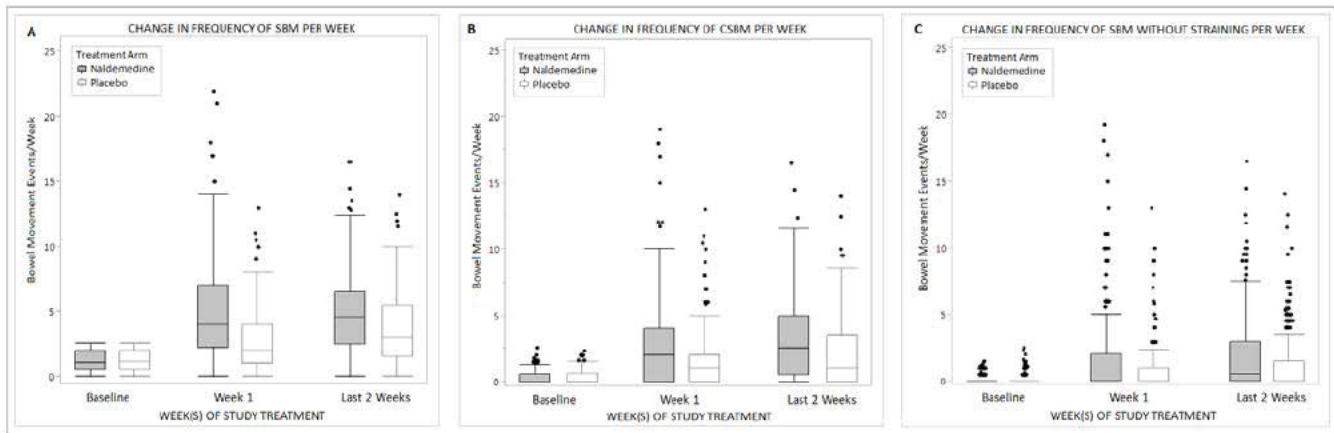
A summary of secondary endpoint analyses for both adjusted and unadjusted BM frequencies are presented in Table 40.

Table 41: Secondary Endpoint Analyses, ITT Population, Study V9232

Statistical Method	Secondary Endpoint (Frequency per Week)	Treatment Arm, LS Mean (SE)		Difference- LS Means (Naldemedine-Placebo)	
		Naldemedine (N=276)	Placebo (N=274)	n (Δ) 95% CI	p-value
Adjusted BM Frequency	Change in SBM: Baseline to Last 2 Weeks	3.56 (0.174)	2.16 (0.174)	1.40 (0.92, 1.88)	<0.0001
	Change in SBM: Baseline to Week 1	3.86 (0.199)	1.69 (0.198)	2.17 (1.63, 2.71)	<0.0001
	Change in CSBM: Baseline to Last 2 Weeks	2.77 (0.166)	1.62 (0.166)	1.15 (0.70, 1.61)	<0.0001
	Change in SBM without Straining: Baseline to Last 2 Weeks	1.85 (0.163)	1.10 (0.162)	0.75 (0.30, 1.19)	0.0011
Unadjusted BM Frequency	Change in SBM: Baseline to Last 2 Weeks	3.31 (0.173)	2.07 (0.172)	1.25 (0.77, 1.72)	<0.0001*
	Change in SBM: Baseline to Week 1	3.70 (0.193)	1.63 (0.192)	2.07 (1.54, 2.60)	<0.0001*
	Change in CSBM: Baseline to Last 2 Weeks	2.63 (0.165)	1.58 (0.164)	1.05 (0.60, 1.50)	<0.0001*
	Change in SBM without Straining: Baseline to Last 2 Weeks	1.81 (0.162)	1.09 (0.161)	0.72 (0.28, 1.17)	0.0014*

(Source: Reviewer's table)

Figure 13: Frequency of BM Events (SBM, CSBM, and SBM without Straining) at Baseline, Week 1 and the Last 2 Weeks of the Treatment Arm for the ITT Population of Study V9232



(Source: Reviewer's figure)

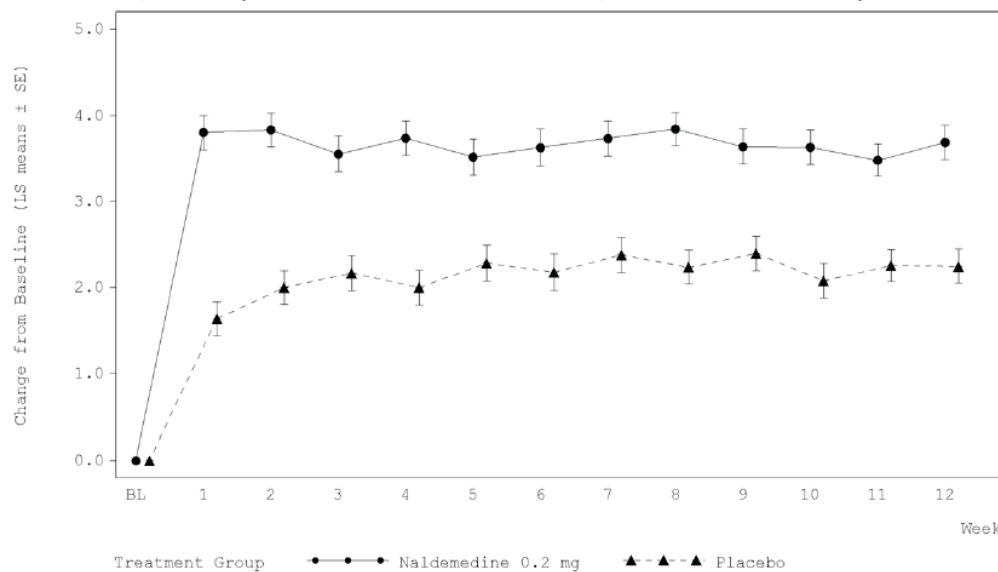
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Dose/Dose Response

Only 1 naldemedine dosage (0.2 mg once daily) was evaluated in controlled phase 3 clinical trials, including Study V9231. Therefore, analyses of dose-response are limited to the phase 2 clinical trial (see Section 5.5.2).

Durability of Response

Figure 14: Change in the Frequency of Spontaneous Bowel Movements per Week from Baseline to Each Week (Least-Squares Mean $\pm$ Standard Error) – Intent-to-Treat Population



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(Source: Applicant's Figure 11-1, "Change in the Frequency of Spontaneous Bowel Movements per Week from Baseline to Each Week (Least-Squares Mean $\pm$ Standard Error) – Intent-to-Treat Population", Clinical Study Report: 1315V9232, page 93/1630)

Persistence of Effect

The half-life of naldemedine is relatively short, and there is no evidence to suggest that treatment effects would persist after stopping the drug.

Additional Analyses Conducted on the Individual Trial

Rescue Medication Use

During the screening period (i.e., baseline), mean ($\pm$ SD) frequency of rescue laxative use was 1.59 ($\pm$ 1.42) doses/week in the naldemedine group and 1.64 ($\pm$ 1.41) doses/week in the placebo group (range 0 to 7 doses for both groups).

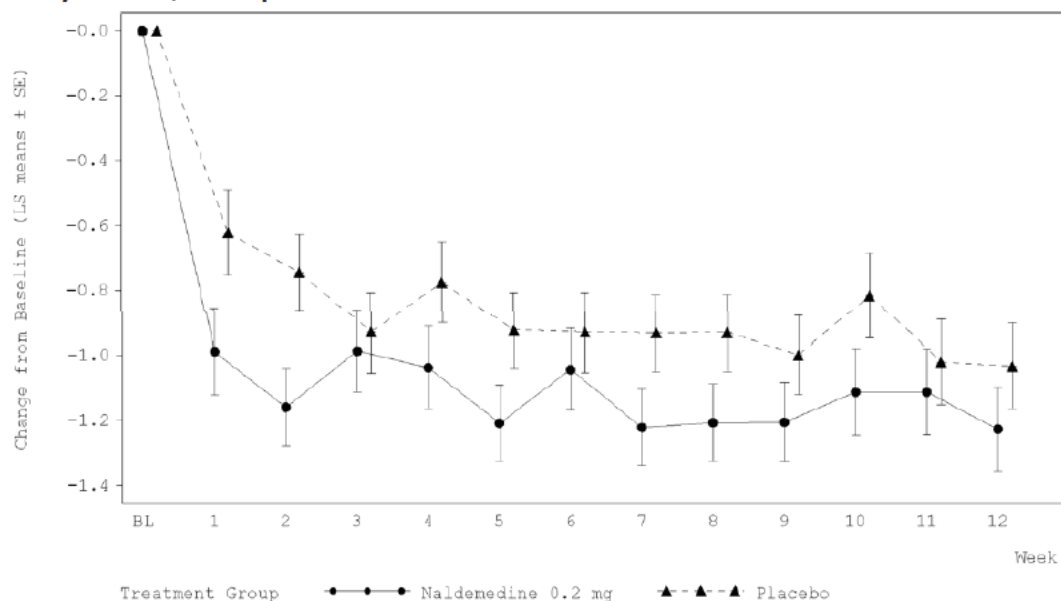
During the treatment period, 165 subjects (59.8%) in the naldemedine arm of the ITT

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population reported rescue medication use (≥ 1 dose), compared to 199 subjects in the placebo arm (72.6%). On the other hand, no rescue laxative use was reported in 91/246 subjects (37.0%) in naldemedine arm with ≥ 8 weeks of data vs. 68/241 subjects (28.2%) in the placebo group with ≥ 8 weeks of data.

A graph of the change in frequency of rescue laxative use per week from baseline (LS mean $\pm$ SE) to each study week by treatment arm is shown in Figure 15.

Figure 15: Change in the Frequency of Rescue Laxative Use per Week from Baseline (LS mean $\pm$ SE) in Study V92232, ITT Population



(Applicant's Figure 11-3, "Change in the Frequency of Rescue Laxative Use per Week from Baseline to Each Week (Least-Squares Mean $\pm$ Standard Error) – Intent-to-Treat Population", Clinical Study Report: 1315V9232, page 101/1630)

Table 42: Frequency of Rescue Medication Use (Doses/Week) for the ITT Population of Study V9232

		Naldemedine (N=273)	Placebo (N=272)
Baseline (Screening Period)	Mean $\pm$ SD	1.59 $\pm$ 1.42	1.64 ($\pm$ 1.41)
	Median	1.27	1.50
	Min – Max	0 – 7	0 – 7
Treatment Period	Mean $\pm$ SD	0.58 $\pm$ 1.25	0.82 $\pm$ 1.34
	Median	0	0
	Min – Max	0 – 7	0 – 7
Last 2 weeks	Mean $\pm$ SD	0.55 $\pm$ 1.26	0.71 $\pm$ 1.27
	Median	0	0
	Min – Max	0 – 7	0 – 7

(Source: Reviewer's Table)

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Subject Global Satisfaction (SGS) Scores

A Subject Global Satisfaction evaluation was completed at Visit 7 (Week 12)/Early Termination, by 396 subjects in the ITT population (72.0%)—204 subjects in the naldemedine group (73.9%) and 192 subjects in the placebo group(70.1%). Results are shown in Table 26.

In the naldemedine group, 162 of the 204 subjects with completed assessments (79.4%) had scores 5-7 (i.e., markedly, moderately, or slightly improved), compared with 110/192 subjects (57.3%) in the placebo group (nominal $p < 0.0001$).

As discussed in Section 6.2.2, these data were also used for assessments of the clinical meaningfulness of secondary endpoint data. CDF plots for Study V9232 are found in the Appendix, Section 13.4, and are discussed in Section 7.1.3.

Table 43: Subject Global Satisfaction Scores for the ITT Population of Study V9232

SGS Score	Naldemedine (N=204)	Placebo (N=192)
Markedly Improved (7)	72 (35.3)	32 (16.7)
Moderately Improved (6)	53 (26.0)	39 (20.3)
Slightly Improved (5)	37 (18.1)	39 (20.3)
Unchanged (4)	28 (13.7)	54 (28.1)
Slightly Worsened (3)	3 (1.5)	12 (6.3)
Moderately Worsened (2)	5 (2.5)	10 (5.2)
Markedly Worsened (1)	6 (2.9)	6 (3.1)

(Source: Adapted from Table 14.2-3.13 in Section 14.2 of the Clinical Study Report: 1315V9232, page 742/1630)

Changes in Total and Free Testosterone in Males

The changes in total and free testosterone in males from baseline to Visit 7 (Week 12)/Early Termination for the naldemedine group were small and not meaningfully different from the placebo group.

6.3. Study V9235

6.3.1. Study Design

Introductory Comment: Study V9235 was conducted primarily to assess the long-term safety of naldemedine. Evaluation of efficacy was a secondary objective, and therefore, the efficacy data from Study V9235 are viewed as supportive. Furthermore, the trial design of Study V9235 introduced potential confounders of efficacy data interpretation, particularly with respect to allowable concomitant medications and rescue laxative use that were not included in Studies V9231 and V9232. The broader range of medications permitted during participation in this 52-

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week safety trial is understandable in an effort to maintain enrollment in long-term placebo-blinded studies.

Overview and Objective

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Phase 3 Study to Evaluate the Long-Term Safety of Naldemedine for the Treatment of Opioid-Induced Constipation in Subjects with Non-Malignant Chronic Pain Receiving Opioid Therapy

Study V9235 was designed primarily as a long-term safety trial. Although the Applicant included efficacy assessments, this study did not have any primary efficacy objectives.

Trial Design

Title: A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Phase 3 Study to Evaluate the Long-Term Safety of Naldemedine for the Treatment of Opioid-Induced Constipation in Subjects with Non-Malignant Chronic Pain Receiving Opioid Therapy

The primary objective of study V9235 was to assess the overall safety and tolerability of naldemedine in subjects with non-malignant chronic pain receiving a stable opioid therapy regimen for ≥ 1 month and having opioid-induced constipation (OIC).

Study Population

Approximately 1200 subjects were to be randomized in a 1:1 ratio to either the naldemedine or placebo treatment arm (600 subjects each).

The original target study population was 1500 subjects but was reduced to 1200 subjects.

Reviewer Comment: For Study V9235, the data analyses for NDA submission (both safety and efficacy) were conducted using data from the "Core Period Data Set" (data cut-off date 24 June 2015). As of this data cut-off date, 747/1241 subjects in the ITT population (60.2%) had reached study completion/termination (376 in the naldemedine arm and 369 in the placebo arm). For the 496 subjects with ongoing study participation at the end of the Core Period, all had completed

Efficacy analyses were conducted using data from the Core Period.

Study Eligibility

Subject eligibility requirements with respect to OIC-related baseline characteristics and disease severity were the same as Studies V9231 and V9232. Subjects must have had self-reported OIC a and a documented medical history indicating non-malignant chronic pain for at least 3 months' duration and a stable opioid regimen with an average total daily dose of ≥ 30 mg equivalents of oral morphine sulfate for at least 1 month prior to the Screening Visit.

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Like Studies V9231 and V9232, subject eligibility and SBM status (i.e., frequency of SBMs) were based on a 14-consecutive-day qualifying period during the 28-day Screening Period. Subjects must have recorded at least 4 days of BM data for each 7-day period that constituted 1 week in the electronic diary (eDiary). Subjects who did not meet the eligibility criteria during the first 14 days of the Screening Period may have continued for up to 28 days to allow them to meet the eligibility criteria. No more than 4 SBMs total over the 14-consecutive-day qualifying period were allowed. In addition, no more than 3 SBMs in a given week of the qualifying period were allowed.

Subjects were not required to be on a stable laxative regimen to be eligible for participation in study V9235. Subjects with a stable laxative regimen prior to enrollment were permitted to stay on their regimen for the duration of the study.

With the exception of laxative medication use, inclusion and exclusion criteria for Study V9235 were the same as Studies V9231 and V9232.

Study Treatment

Subjects were randomized in a 1:1 ratio to receive a single tablet of either 0.2 mg of naldemedine or placebo (600 subjects each) QD in a double-blind manner for 52 weeks. At the time of randomization, subjects were stratified based on their documented opioid use (average TDD during the 14-consecutive-day qualifying period) as follows:

- 30 to 100 mg equivalents of oral morphine sulfate (average TDD)
- 100 mg equivalents of oral morphine sulfate (average TDD)

The naldemedine formulation used in Study V9325 was the same as used in other Phase 3 clinical trials, a tablet for oral administration, containing 0.2 mg of the active compound. Placebo tablets were identical to active tablets in appearance, taste, color, and odor. The study drug (and placebo) was dispensed using the same procedures as Studies V9231 and V9232.

Treatment Compliance:

Assessments of treatment compliance by the Investigator and/or site personnel were performed during each study visit, including:

- Tablet counts performed by qualified site personnel to verify that the correct number of doses were taken based on the actual number of days that had elapsed between clinic visits
- Information provided to the Investigator/staff by the subject during Study Visits
- eDiary records (only collected for the first 14 days of the Treatment Period)

If noncompliance with study medication was identified, site personnel were supposed to counsel subjects, and if non-compliance persisted (dosing compliance <80%), the subject was to be withdrawn from the study. In the event that a subject was withdrawn for compliance reasons, the Investigator was responsible for notification of the Application or designee and to CDER Clinical Review Template 2015 Edition
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make every effort to complete the Early Termination assessments and the Early Termination/Study Completion eCRF. All subject discontinuations were supposed to be registered in the IVRS/IWRS system.

Prior and Concomitant Therapy

All medications (prescription and over-the-counter) taken by the subject for 3 months prior to Screening, and concomitant medications taken with the study drug through the end of the study were recorded in the CRF.

Concomitant Opioid Therapy

By definition of the study population, all subjects enrolled in this study were receiving opioid therapy for chronic, non-cancer pain. To be eligible for study participation, a subject was required to have been treated with opioids for ≥ 3 months, with a stable opioid regimen at a TDD on average of ≥ 30 mg equivalents of oral morphine sulfate for ≥ 1 month prior to Screening and without anticipated changes in their overall opioid regimen during study participation. Opioid therapy was not provided as part of the study, as subjects were required to be on a stable opioid regimen prior to the Screening Visit.

Subjects were permitted to take additional medication (opioid or non-opioid) for breakthrough pain as prescribed by their physician. At the screening visit, all opioid medication(s) taken by the subject during the prior 3 months were recorded on the eCRF. All pain medication(s) (opioid or non-opioid) were recorded by the subject throughout the study.

Use of tramadol and tapentadol were permitted in this study. Tramadol and tapentadol have a dual mechanism of action, including opioid-mediated analgesia. However, these medications are considered weak opioids and are associated with less constipation than other opioids. Therefore, to ensure that subjects were receiving an adequate opioid dose, tramadol and tapentadol were not included in the calculations for either the stable opioid regimen at a TDD on average of ≥ 30 mg equivalents of oral morphine sulfate for eligibility assessment, or stratification by average TDD.

Laxative Therapy

Unlike Study V9231 and Study V9232, discontinuation of laxatives was not an eligibility criterion for Study V9235. However, subjects were required to be on a stable laxative regimen prior to study enrollment. To be eligible for study participation, the subject was required to meet the OIC diagnostic criteria defined by SBM frequency, regardless of laxative use.

For subjects who were not taking laxatives regularly at Screening, the laxative regimen for the 28 days prior to Screening was used as the “established laxative regimen.” To avoid fluctuations in OIC severity, subjects were supposed to maintain their established regimen without dosage changes throughout the Screening Period and Treatment Period. Any BMs that

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occurred on the established laxative regimen were counted as SBMs. For subjects without regular laxative use at Screening, laxative use during the Screening and Treatment Periods was documented as rescue laxative treatment.

Subjects were allowed to use a rescue laxative after 72 hours without a BM. In this situation, subjects with established laxative regimens used medications/dosages that were different from their regular regimen. Subjects who were taking laxatives regularly at Screening were instructed to re-establish their baseline regimen as soon as possible after rescue laxative use. Any BM that occurred within 24 hours of rescue laxative use was not counted as an SBM. If subjects did not have a BM for 5 days, they were instructed to call the clinical site Investigator.

During the Screening Period, use of rescue laxative was recorded in the eDiary; during the Treatment Period, subjects' laxative use was reviewed at each study visit and documented in the eCRF by study site personnel. Unlike Study V9231 and V9232, subjects did not maintain regular diary records of rescue laxative use.

It is important to note that rescue medication use during the Treatment Period was not recorded. Therefore, SBM frequency was only used as a baseline assessment to establish study eligibility. For efficacy assessments, BM frequency (i.e., number of BM events during the specified 7-day period, irrespective of rescue laxative use) was used as the outcome variable.

Reviewer Comment: The Applicant permitted concomitant use of maintenance laxatives during this study with the expectation that subject would maintain these regimens throughout study participation. Study V9235 was primarily a long-term safety study whose success depended on the ability to compile a safety database with adequate study drug exposure, which can be particularly challenging for long-term placebo-controlled trials. Loosening of concomitant medication restrictions to allow maintenance laxative use likely helped facilitate recruitment and retention of study subjects. However, interpretation of efficacy assessments is limited by this study design choice.

For 18% of the study population, concomitant laxative use did not comply with the procedures and definitions described above. Study data of laxative use will be discussed in more detail in Section 6.3.2. The purpose of this review comment is to convey that the procedures described above do not accurately reflect actual concomitant laxative use during the conduct of the study. Subjects with changes in maintenance laxative use from baseline were not excluded from study participation or analysis datasets. As a safety trial, no mITT or PP datasets were defined for Study V9235. In retrospect, the expectation that subjects maintain the same laxative regimen for the entire treatment duration may not have been reasonable. However, these deviations from study procedures present a major confounder for efficacy analyses, and the Applicant did not follow pre-specified or consistent procedures for handling these subjects' disposition and study data.

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To address the issue of concomitant laxative use, the Applicant defined 3 post-hoc analysis datasets (no laxative, stable, and “other”) based on subjects’ baseline laxative regimen and concomitant laxative use study participation, whereby the “other” subgroup was comprised of subjects who did not meet criteria for either of the other 2 subgroup, and is heterogeneous with respect to both subjects’ baseline laxative regimens and the types of changes made to laxative use during study participation.

Prohibited Concomitant Medications (same as Study V9231 and Study V9232)

Prohibited medications were not to be taken by subjects at any time during the study. Use of prohibited concomitant therapy could have resulted in study discontinuation. Prohibited medications included but were not limited to the following:

- Opioid antagonists (alvimopan, methylnaltrexone bromide)
- Acetylcholine agonists (bethanechol)
- Guanylate cyclase-C agonist (linaclotide)
- 5-HT-4 agonists (prucalopride)
- Prostaglandin (misoprostol)
- Mu receptor partial agonist opioids (meptazinol)
- Mixed agonist/antagonist (nalorphine-like agonist/antagonist opioids) (pentazocine, buprenorphine)
- Antispasmodics (dicyclomine)
- Antidiarrheals (loperamide)
- Prokinetics (metoclopramide)
- Chloride channel activator (lubiprostone)

Any additional medications that could have had a significant impact on the GI system or bowel habits may have been prohibited at the Investigator’s discretion.

Other Restrictions

Subjects were not to initiate any new diets, supplement changes, or exercise regimens after Screening and throughout the study.

Study Endpoints

The efficacy measures in Study V9235 were specified as secondary and exploratory endpoints.

➤ Secondary Endpoints:

- Change in the frequency of BMs from baseline to selected time points of the Treatment Period
- Number of subjects with laxative use
- Change in the Patient Assessment of Constipation Symptoms (PAC-SYM) Overall Score from baseline to each visit
- Change in the PAC-QOL Overall Score from baseline to each visit

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- Frequency of Subject Global Satisfaction by treatment group
- Exploratory endpoint: total and free testosterone levels in male subjects

Of the secondary efficacy endpoints specified for Study V9235, only change in the frequency of BMs from baseline to selected time points of the Treatment Period is aligned/ comparable with the primary and major secondary endpoints of Studies V9231 and V9232. In addition, analyses of laxative use in Study V9235 are not comparable to rescue medication data from Studies V9231 and V9232 due to differences in study design which allowed concomitant use of laxatives, even if regimens were not stable prior to enrollment.

Reviewer Comment: In Study V9235, rescue medication data was recorded by clinical trial site personnel at study visits and used only as an independent efficacy variable. Data regarding the timing of rescue medications with respect to BM events to determine SBM frequency was only captured during the Screening Period to determine eligibility based on OIC diagnostic criteria. The outcome variable used for efficacy analysis was BM frequency, which included all BM events, irrespective of rescue laxative use. However, inclusion of BM events that required the aid of rescue medication confounds assessments of the effectiveness of treatment and need to be interpreted cautiously.

Study Procedures

The schedule of procedures for Study V9235 is shown in Table 43.

In Study V9235, an eDiary with procedures similar to those used in Studies V9231 and V9232 was used only during the Screening Period. During the Treatment Period, a “Bowel habits” patient (paper) diary was used for the pre-specified 7-day efficacy assessment periods prior to Weeks 12, 24, 36, and 52. Opioid and laxative use data were captured by study personnel during study visits.

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Table 44: Schedule of Assessments in Study V9235

Evaluation	Screening Period	Treatment Period													Follow-Up Period	Early Termination	Unscheduled Visit	
	Visit 1 up to-28 days prior to randomization (min 14 days)	Visit 2 Day 1 Within 7 days of qualification	Visit 3 Wk 1 ± 3 days	Visit 4 Wk 2 ± 3 days	Visit 5 Wk 6 ± 3 days	Visit 6 Wk 12 ± 3 days	Visit 7 Wk 18 ± 7 days (phone)	Visit 8 Wk 24 ± 7 days	Visit 9 Wk 30 ± 7 days (phone)	Visit 10 Wk 36 ± 7 days	Visit 11 Wk 42 ± 7 days (phone)	Visit 12 Wk 48 ± 7 days	Visit 13 Wk 52 ± 7 days	Visit 14 Wk 54 ± 7 days				
Informed Consent	X																	
I/E Criteria	X	X																
Demographics	X																	
Medical History	X	X																
Bowel Habits Diary	X					X		X		X		X		X		X		X
Physical Examination	X	X	X	X	X	X		X		X		X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X		X		X		X	X	X	X	X	X	X
12-Lead ECG	X							X					X				X	
Hematology	X	X			X	X		X		X		X	X	X	X (pm)	X		X
Serum Chemistry	X	X			X	X		X		X		X	X	X	X (pm)	X		X
Serum Hormones	X	X				X							X	X (pm)	X		X	
HA,HBsAg,HCV	X																	
Pregnancy Test Serum or Urine	Serum	Urine				Urine		Urine		Urine		Urine	Urine	Urine	Urine	Urine		
Urinalysis	X	X				X		X					X	X (pm)	X		X	
Dipstick Urinalysis					X					X		X						
Randomization		X																
Drug Accountability			X	X	X	X		X		X		X	X	X	X		X	
Study Drug Dispensation		X		X	X	X		X		X		X						
CV Event Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Med Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
COWS		X	X	X	X	X		X		X		X	X		X		X	
SOWS		X	X	X	X	X		X		X		X	X		X		X	
PAC-SYM/ PAC-QOL		X		X		X		X		X			X				X	
11-Point NRS		X	X	X	X	X		X		X		X	X	X	X	X	X	X
Subject Global Satisfaction													X				X	
Early Termination/ Study Completion form													X				X	

(Source: Applicant table 9-2, "Schedule of Events", Clinical Study Report: 1326V9235, page 54-56/2798)

Statistical Analysis Plan

Change in Frequency of BMs per Week

Efficacy endpoints were the secondary endpoints of the study. For comparison between treatment groups, the significance level of tests was set at 0.05 (2-sided).

The change in the frequency of BMs from baseline to selected time points of the Treatment Period was summarized using the same definition for frequency of BMs per week (derived from the number of reported BMs, adjusted for the number of eDiary entries with defecation information) as used in Studies V9231 and V9232.

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Using this definition, the change in the frequency of BMs per week from baseline to each selected visit [(Frequency of BMs per week for each selected visit) – (Frequency of BMs per week in baseline period)] was calculated.

The mean change in frequency of BMs per week from baseline to each selected visit was compared between naldemedine and placebo using a mixed-effects repeated measures (MMRM) method which included the opioid dose strata as a covariate and treatment group, time, and time-by-treatment group interaction as fixed effects. Plots of least-square means of the changes (and their standard error) over time were presented by treatment group.

Number of Subjects with Laxative Use

Descriptive statistics of laxative use during study participation (i.e., number and proportion of subjects) were summarized with respect to baseline laxative regimen. Rescue laxative was defined as any laxative that subjects started to take during the Treatment Period.

PAC-SYM and PAC-QOL scores

The change in PAC-SYM and PAC-QOL scores (mean overall score and scores for individual domain) from baseline to each visit was calculated and summarized for each treatment group.

Frequency of Subject Global Satisfaction

Subject global satisfaction was graded at Visit 13 or early termination using the following 7-point grading scale:

- 1 = markedly worsened
- 2 = moderately worsened
- 3 = slightly worsened
- 4 = unchanged
- 5 = slightly improved
- 7 = markedly improved

Subject global satisfaction grades were tabulated by treatment group. The proportion was also summarized by treatment group and compared between naldemedine and placebo using the Wilcoxon rank sum test.

Subgroup Analyses

Subgroup analyses for the secondary endpoints were performed for the subgroups not on a stable laxative regimen, defined as subjects who did not have a laxative from the 28 days prior to the Screening Period to the final dose of study drug or who received only laxative as rescue at least once, and the subgroup on a stable laxative regimen.

Reviewer's Comment: As previously noted above, BM frequency (i.e., number of BM events,

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irrespective of rescue laxative use) was the only type of BM-related outcome variable used for efficacy analyses in Study V9235. SBM frequency was not used because data regarding the use and timing of rescue laxatives with respect to BM events was not collected. In Study V9235, on-treatment diary records were only required during the 4 week-long efficacy assessment periods and did not distinguish BM events based on whether rescue laxative use was required for passage. While this reviewer acknowledges that the daily eDiary requirements used in the 2 shorter clinical trials would have been too demanding for the full duration this long-term trial, treatment effect cannot be adequately assessed based BM event frequency that does not account for rescue medication use.

Protocol Amendments

Three protocol amendments were applied to the original protocol for Study V9235, dated 09 July 2013.

- Amendment 1: 07 October 2013
- Amendment 2: 16 June 2014
- Amendment 3: 26 February 2015

The key changes implemented with the V9235 protocol amendments included the following:

Amendment 1

- Added a serum pregnancy test at Visit 2 (Day 1) prior to dosing for all females of childbearing potential
- Added directions for collecting data for laxative use during the Treatment Period at study site visits and recording the data on the CRF
- Added directions for recording all opioid pain medication(s) dosing daily in the eDiary during the Screening Period and for the first 2 weeks of the Treatment Period
- Added directions that opioid therapy was then to be captured on the CRF throughout the entire duration of the study
- Added list of prohibited medications that were not to be taken by subjects at any time during the study
- Specified that the Visit 8 (Week 24) safety data would be analyzed by the DSMB.

Amendment 2

- Added text to the synopsis and inclusion criteria stating that subjects must meet the following criteria based on an eDiary to be completed over a 14-consecutive-day qualifying period during the 28-day Screening Period: No more than 4 SBMs total over the 14-consecutive-day qualifying period. In addition, no more than 3 SBMs in a given week of the qualifying period.

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- Added text to Section 3.1 to specify that subjects might use laxatives during the Screening Period.
- Added text to specify that tramadol and tapentadol would not be used in the calculations for either inclusion criterion #3, calculation of the stable opioid regimen at a total average daily dose of ≥ 30 mg equivalents of oral morphine sulfate, or for stratification by average daily dose of 30 to 100 mg equivalents of oral morphine sulfate versus >100 mg equivalents of oral morphine.
- Specified that use of tramadol and tapentadol was allowed in the trial but only in conjunction with other opioid agonists
- Added subheading 7.7.1.1 stating that the change in frequency of BMs from baseline to selected time points in the Treatment Period was to be assessed as an efficacy endpoint. Subjects were to monitor BMs during the 52-week Treatment Period and will be asked to complete the Bowel Habits paper diary. Also, during the Treatment Period, subjects were to record BM data on the paper diary during the week prior to each of the selected study visits (ie, Bowel Habits paper diary should have been filled out during the Weeks of 11, 23, 35, and 51, corresponding to the week prior to Study Visits 6, 8, 10 and 13, respectively).

Amendment 3

- Wording of the primary objective was changed to “Assess the overall safety and tolerability of naldemedine in subjects with non-malignant chronic pain receiving a stable opioid therapy regimen for ≥ 1 month and having OIC.”
- The sample size was changed as follows: “Approximately 1200 subjects will be randomized in a 1:1 ratio to receive a single tablet of either 0.2 mg of naldemedine or placebo (600 subjects each) QD in a double-blind manner during the 52-week Treatment Period.” This change was made per agreement with the US FDA and per alignment with ICH Guidance E1, The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions. Exposures of at least 300-600 subjects for 6 months and 100 subjects for 1 year in each of the study arms is *[sic]* anticipated.”
- The following text was added to Section 3.1 Overall Study Design and Plan:
 - “For analysis purposes, data from the Treatment Period will be divided into a Core Period Data Set and a Supplemental Period data set. The Core Period Data Set will consist of all subjects with at least 24 weeks of treatment (i.e., up to and including Visit 8, Week 24 at a minimum). Some subjects in the Core Period Data Set will have greater than 24 weeks of treatment (i.e., up to 12 months). The Supplemental Period data set will consist of all remaining data (i.e., study visits not completed at the time of the Core Period data lock).

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- The separation of the Treatment Period into the Core Period Data Set and the Supplemental Period data set does not impact study conduct or subjects. Study visits and the Schedule of Events remain as presented (Appendix 1).”
- Section 5.5 Blinding was changed to read as follows: “All subjects, the Investigator, all study personnel, and data analysts will be blinded to the treatment assigned at randomization until database lock. Treatment assignments for the [study medication] will be concealed by the use of identical packaging, labeling, dosing instructions, appearance, taste, color, and odor.”
- The following text was added to Section 5.5.1 “Unblinding: Following the database lock for the Core Period, the Sponsor will be unblinded to the randomization codes. All subjects, the Investigator, and study site personnel will remain blinded.
- In Section 7.7, “(Efficacy) Assessments” was changed to “Secondary (Efficacy) Assessments”.
- Section 8.4.3 Early Termination was changed to specify that subjects who terminated early should also have a Follow-up Period Visit (Visit 14; Section 8.4.2), 2 weeks after their last dose of study drug.
- The following wording was added to Section 9.1 General Considerations:
 - “The Core Period Data Set will consist of all subjects with at least 24 weeks of treatment (ie, up to and including Visit 8, Week 24 at a minimum). Some subjects included in this data set will have completed more than 24 weeks of treatment. The Core Period Data Set is considered a complete and “stand alone” data set that will be used for Global Registration purposes. The Supplemental Period data set will consist of all remaining data (i.e., study visits not completed at the time of the Core Period data lock). For Statistical purposes, a Combined data set will also be compiled that will consist of the Core Period and the Supplemental Period.”
- In Section 9.9.1 Primary Endpoint, the primary endpoint was changed from the number of Major Cardiovascular Events (MACE) during a 52-week Treatment Period to “Safety: The incidence of TEAEs, SAEs, and AEs leading to discontinuation. AEs will be classified by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) Version 16.0. TEAEs will be used for safety analyses. The definition of TEAE is an AE which occurs from first dose of study drug until 14 days after last study dose.”
- Section 9.9.4 Adverse Events of Special Interest was added to the protocol:
 - “Section 9.9.4.1 Major Adverse Cardiovascular Events (MACE): The number and percentage of subjects with Major Adverse Cardiovascular Events (MACE) will be summarized by treatment group. Incidence rate of MACE will also be presented. These events will be summarized by the stratified opioid dose groups and treatment group. Major Adverse Cardiovascular Events were defined as cardiovascular death, myocardial infarction, and cerebrovascular accident.

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- Section 9.9.4.2 Assessment of Opioid Withdrawal: Identification of possible opioid withdrawal events will come from multiple sources, including: AE terms (e.g. DSM-V criteria and SMQ terms), Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), and Pain assessment [11-Point Numeric Rating Scale, opioid dose]. The number and the percentage of subjects with possible opioid withdrawal based on AE terms will be summarized by treatment group. Summary statistics for continuous variables such as COWS will be presented for each scheduled time point and for change from baseline to each time point.”

6.3.2. Study Results

Compliance with Good Clinical Practices

The Applicant reported that operating procedures and audit programs were by the CRO and Applicant in accordance with the Good Clinical Practice (GCP) guidelines, as documented by the International Conference on Harmonization (ICH) and the FDA.

Financial Disclosure

None of the site investigators who participated in this clinical trial had disclosable financial information. Additional details are provided in Section 13.2.

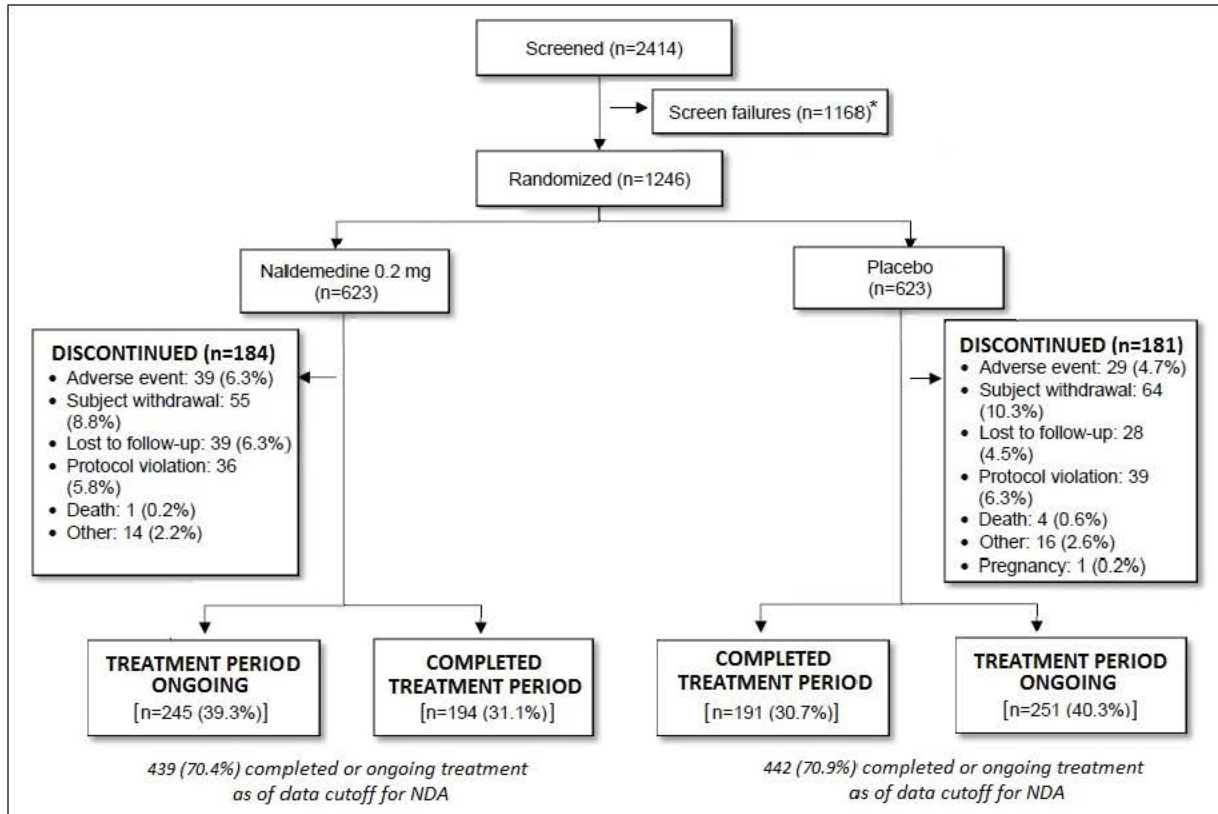
Subject Disposition

The subject disposition for all enrolled and screened subjects as of the data cutoff date for NDA submission (the Core Data Set) is shown in Figure 17. The dropout rates for the 2 treatment arms are similar (31.1% for the naldemedine arm vs. 30.7% for the placebo arm). Of note, the observed dropout rate is similar to rates observed in other long-term trials for OIC, as noted by the Division during the Type C meeting in October 2014, held to discuss the trial design of Study V9235.

Five randomized subjects in Study V9235—2 subjects randomized to the naldemedine arm (Subject IDs 52341-001 and 52344-007) and 3 subjects randomized to the placebo arm (Subject IDs 52311-004, 52344-005, and 52357-001) were excluded from the V9235 ITT and safety populations because they were also enrolled in another naldemedine clinical trial.

All efficacy analyses submitted for Study V9231 were performed using the Core Period Dataset. Unlike safety analyses, efficacy analyses were not conducted using data accrued during the Supplemental Period. However, the Applicant continued to conduct planned efficacy assessments during the Supplemental Period, and the additional efficacy data accrued during this period were submitted as part of the Supplemental Period datasets.

Figure 16: Subject Disposition for All Randomized Subjects in Study V9235, as of the Core Period Data Cut-off Date (24 June 2015)

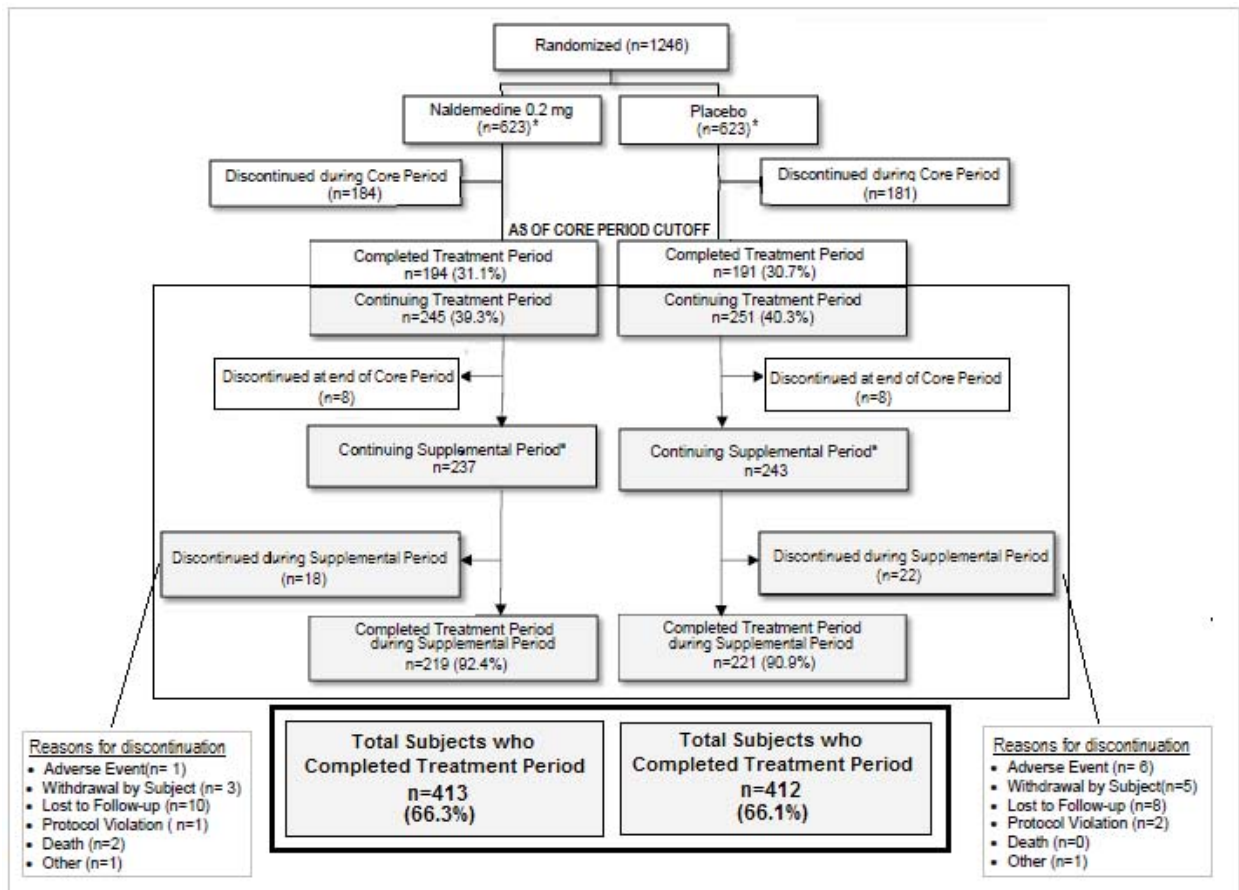


(Source: Adapted from Applicant's Figure 10-1, "Consort Diagram for Subject Disposition- All Subjects Enrolled", page 70/2796, Clinical Study Report: 1326V9235; NDA 208854, Module 5.3.5.1)

* Reasons for screen failure: (n=1168)

- eDiary eligibility (n=402)
- eDiary compliance (n=101)
- Positive urine drug screen (n=53)
- Screening lab test (n=1)
- Medical history (n=87)
- Unstable opioid regimen (n=51)
- Prohibited concomitant medication (n=13)
- Lab results (n=149)
- Other (n=311)

Figure 17: Subject Disposition for all Randomized Subjects in Study V9235 (Entire Study Duration)

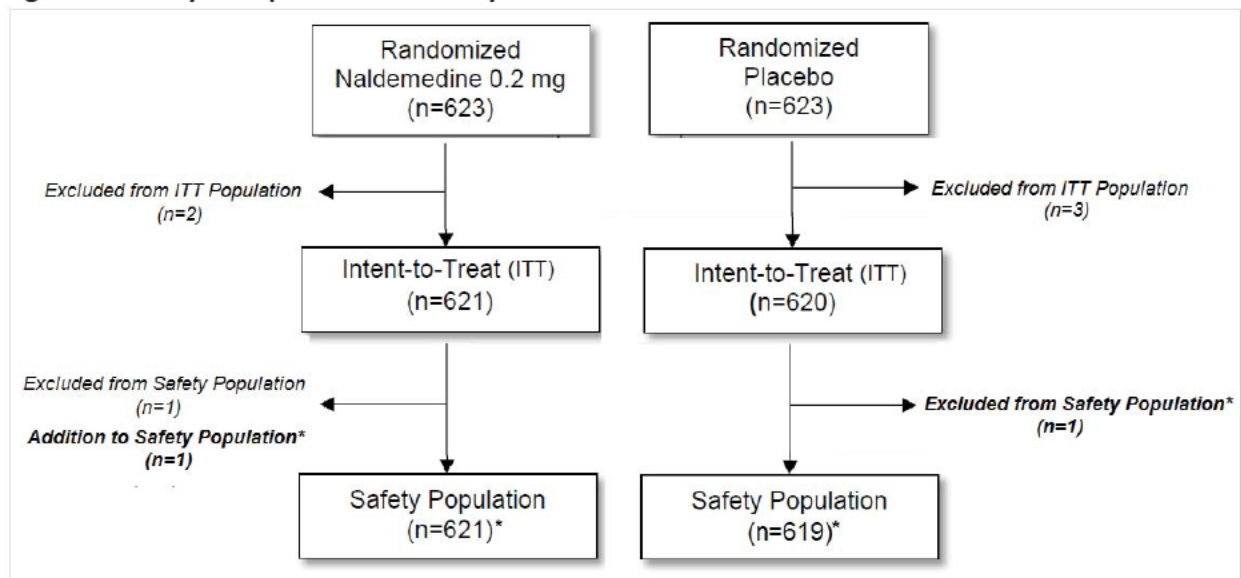


(Source:

During the Supplemental Period, the number (percentage) of subjects who discontinued from the study was similar in both treatment groups (7.6% in the naldemedine group and 9.1% in the placebo group) and the reasons for discontinuation were also generally similar between groups.

Of the subjects continuing in the Supplemental Period, a similar proportion of subjects completed the 52-week Treatment Period in both treatment groups (naldemedine, 92.4%; placebo, 90.9%).

Figure 18: Analysis Populations for Study V9235



(Source: Applicant’s Figure 10-2, “Consort Diagram for Analysis Populations – All Randomized Subjects”, Clinical Study Report: 1326V9235, page 72/2796)

Table 45: Randomized Subjects Excluded from Analysis Populations in Study V9235

Analysis Population [†]	Reason for Exclusion*	Treatment Arm	
		Naldemedine (N=623)	Placebo (N=623)
ITT	Double enrollment at different study sites	2	3
Safety	No study drug administered during treatment period	1	0
	Received wrong study drug	0	1*

(Source: Reviewer’s table based on analysis data, NDA 208854 Module 5.3.5.1)

Protocol Violations/Deviations

320 subjects (>50%) had ≥1 major protocol deviation (163 naldemedine, 157 placebo). 31 with 2 (14 naldemedine, 17 placebo). Rest had 1. Most common was prohibited med use, which represents another reason for limited applicability of efficacy data from this trial.

Table 46: Major Protocol Deviations for Randomized Subjects in Study V9235

Type of Major Protocol Deviation	Naldemedine (N=623)	Placebo (N=623)
Any major protocol deviation	163 (26.2)	157 (25.2)
Prohibited medication/therapy during treatment period	73 (11.7)	84 (13.4)
Medication compliance <80% or >120%	69 (11.1)	59 (9.5)
< 30 mg opioid on average during treatment period	15 (2.4)	12 (1.9)
Evidence of active medical diseases affecting bowel transit [†]	14 (2.2)	11 (1.8)
Evidence of significant structural abnormalities of the GI tract [‡]	4 (0.6)	4 (0.6)
Double enrollment at different sites per subject	2 (0.3)	3 (0.5)
Administration of incorrect drug	1 (0.2)	1 (0.2)
No study drug administration during treatment period	1 (0.2)	0

(Source: Reviewer's table based on analysis data, NDA 208854 Module 5.3.5.1)

Abbreviations in table:

[†]e.g., ileus, uncontrolled hypothyroidism, IBS, inflammatory bowel disease, fecal incontinence

[‡]history of bowel obstructions, strictures; and history of bowel surgery such as bowel resection or bariatric surgery

Demographic and Baseline Characteristics

Demographics

The demographics for the ITT population of Study V9235 are summarized in Table 46. Although the mean and median ages for the populations are similar, the number of subjects ≥65 years old and ≥75 years old is higher in the naldemedine population. In addition, the naldemedine group also included a slightly higher percentage of male subjects. Similar to the other naldemedine trials, the mean BMI for both groups was in the obese range, and >50% of subjects in both groups were obese. Also similar to other trials, the majority of subjects in Study V9235 were white.

Table 47: Subject Demographics for the ITT Population, Study V9235

Demographic Parameter		Naldemedine (N=621)	Placebo (N=620)	Total (N=1240)
Age (years)	Mean ± SD	53.4 ± 11.7	52.7 ± 10.6	53.0 ± 11.1
	Median	54.0	53.0	54.0
	Range	20 – 80	21 – 79	20 – 80
Age Category (years), n (%)	<40	75 (12.1)	68 (11.0)	143 (11.5)
	>=40 to <65	445 (71.7)	475 (76.7)	920 (74.2)
	>=65	101 (16.3)	76 (12.3)	177 (14.3)
	>=75	22 (3.5)	10 (1.6)	32 (2.6)
Sex, n (%)	Male	238 (38.3)	217 (35.1)	455 (36.7)
	Female	383 (61.7)	402 (64.9)	785 (63.3)
Height (cm)	n	621	619	1240
	Mean± SD	168.8 ± 10.3	168.9 ± 10.0	168.9 ± 10.1
	Median	167.6	168.0	167.7
	Range	143.5 – 198.1	144.0 – 198.1	143.5 – 198.1
Body Weight (kg)	n	621	619	1240
	Mean ± SD	90.6 ± 23.6	90.3 ± 24.2	90.5 ± 23.9
	Median	88.5	86.7	87.5
	Range	40.4 – 200.5	41.0 – 197.7	40.4 – 200.5
BMI (kg/m ²)	n	621	619	1240
	Mean ± SD	31.7 ± 7.6	31.5 ± 7.7	31.6 ± 7.6
	Median	30.5	30.3	30.4
	Range	16.0 – 68.2	15.1 – 68.2	15.1 – 68.2
BMI Category (kg/m ²), n (%)	<18.5	6 (1.0)	7 (1.1)	13 (1.0)
	>=18.5 to <25.0	93 (15.0)	96 (15.5)	189 (15.2)
	>=25.0 to <30.0	192 (30.9)	194 (31.3)	386 (31.1)
	>=30.0	330 (53.1)	322 (52.0)	652 (52.6)
Race, n (%)	American Indian or Alaska Native	2 (0.3)	7 (1.1)	9 (0.7)
	Asian	5 (0.8)	7 (1.1)	12 (1.0)
	Black	120 (19.3)	39 (14.2)	88 (16.0)
	Native Hawaiian/ Other Pacific Islander	2 (0.3)	1 (0.2)	3 (0.2)
	White	492 (79.2)	496 (80.1)	988 (79.7)
Ethnicity, n (%)	Hispanic/Latino	47 (7.6)	42 (6.8)	89 (7.2)
	Not Hispanic/Latino	574 (92.4)	577 (93.2)	1151 (92.8)

(Source: Adapted from Applicant’s Table 10-1, “Demographic and Baseline Characteristics –Safety Population”, Clinical Study Report: 1326V9235, pages 74-75/2796)

Other Baseline Disease Characteristics

➤ SBM Frequency

Mean SBM frequency at baseline was the same between treatment arms (Table 47). Twelve subjects in the ITT population, 7 subjects the naldemedine arm and 5 subjects in the placebo arm, had baseline SBM frequency ≥ 3 per week, which exceeds the upper limit specified for study eligibility.

In the placebo arm, baseline SBM frequency was higher in the subjects without baseline laxative use (Table 48). This group also had the lowest proportion of subjects with < 1 SBM/week at baseline.

Table 48: Baseline SBM Frequency for the ITT Population of Study V9235

SBM Frequency		Naldemedine (N=621)	Placebo (N=620)	Overall (N=1241)
Summary Statistics (SBM/week)	Mean $\pm$ SD	1.6 $\pm$ 0.7	1.6 $\pm$ 0.6	1.6 $\pm$ 0.6
	Median	1.6	1.6	1.6
	Range	0 – 7.5	0 – 4.4	0 – 7.5
Categories (SBM/week) n (%)	<1	73 (11.8)	64 (10.3)	137 (11.0)
	≥ 1 to <2	304 (49.0)	288 (46.5)	592 (47.7)
	≥ 2 to <3	237 (38.2)	262 (42.3)	499 (40.2)
	≥ 3	7 (1.1)	5 (0.8)	12 (1.0)

(Source: Adapted from Applicant's Table 10-2, "Spontaneous Bowel Movements per Week at Baseline – Safety Population" Clinical Study Report: 1326V9235, pages 76/2796)

Table 49: Baseline SBM Frequency by Baseline Laxative Use, ITT Population, Study V9235

SBM Frequency		Baseline Laxative Regimen		No Baseline Laxatives	
		Naldemedine (N=410)	Placebo (N=421)	Naldemedine (N=211)	Placebo (N=199)
Summary Statistics (SBM/week)	Mean $\pm$ SD	1.57 $\pm$ 0.63	1.57 $\pm$ 0.63	1.63 $\pm$ 0.73	1.71 $\pm$ 0.58
	Median	1.59	1.50	1.62	1.75
	Range	0 – 3.50	0 – 3.11	0 – 7.50	0 – 4.38
Categories (SBM/week) n (%)	<1	51 (12.4)	54 (12.8)	21 (10.0)	11 (5.5)
	≥ 1 to <2	198 (48.3)	188 (44.7)	106 (50.2)	100 (5.0)
	≥ 2 to <3	168 (41.0)	178 (42.3)	80 (37.9)	84 (42.2)
	≥ 3	3 (0.7)	1 (0.2)	4 (1.9)	4 (2.0)

(Source: Reviewer's table from analysis data, NDA 208854, Module 5.3.5.1)

➤ Opioid Medication Use

Opioid Dose and Type

Baseline TDD of opioids for the ITT population is shown in Table 49. Overall, average dose and distribution of doses is similar between treatment arms. In addition, relative frequencies of individual opioid medications were similar between treatment arms (Table 50), including tramadol and tapentadol (analgesics with dual mechanisms of action, considered weak opioids).

Table 50: Baseline Total Daily Dosage (TDD) of Opioid Medication (mg Morphine Equivalents) in the ITT Population, Study V9235 (N=1241)

		Naldemedine (N=621)	Placebo (N=620)	Overall (N=1241)
Dose (mg)	Mean ± SD	123.0 ± 146.1	121.1 ± 163.4	122.1 ± 154.9
	Median	64.0	60.0	60.0
	Range	0 – 1395.0	0 – 2560.0	0 – 2560.0
	Q1 – Q3	40.0 – 157.5	40.0 – 150.0	40.0 – 150.0
Dose Ranges (mg) n (%)	<30	10 (1.6)	11 (1.8)	21 (1.7)
	>=30 to <=100	378 (60.9)	369 (59.6)	747 (60.2)
	>100 to <=200	131 (21.1)	149 (24.1)	280 (22.6)
	>200 to <=400	77 (12.4)	61 (9.9)	138 (11.1)
	>400	25 (4.0)	29 (4.7)	22 (4.4)

(Source: Adapted from Applicant’s Table 10-3, “Average Total Daily Dose of Opioid at Baseline: Electronic Data Capture Data –Safety Population” Clinical Study Report: 1326V9235, pages 77/2796)

Table 51: Opioid Medications Used by Subjects in the ITT Population of Study V9235

Drug Name	Naldemedine (N=621)	Placebo (N=619)
Oxycodone	265 (42.7)	275 (44.4)
Hydrocodone	237 (38.1)	250 (40.4)
Morphine	177 (28.5)	181 (21.2)
Fentanyl	75 (12.1)	85 (13.7)
Tramadol	59 (9.5)	48 (7.8)
Hydromorphone	47 (7.6)	35 (5.7)
Dihydrocodeine	22 (3.5)	19 (3.1)
Oxymorphone	19 (3.1)	17 (2.7)
Meperidine	7 (1.1)	3 (0.5)
Tapentadol	2 (0.3)	6 (1.0)
Codeine	5 (0.8)	2 (0.3)
Lamaline	4 (0.6)	3 (0.5)
Buprenorphine	3 (0.5)	2 (0.3)
Nalbuphine	2 (0.3)	0

(Source: Reviewer’s table)

➤ Baseline Laxative Use

Unlike Studies V9231 and V9232, concomitant regular laxative use was permitted in Study V9235 if subjects were on a stable laxative regimen for at least 28 days prior to screening. A stable laxative regimen was defined as regular use of ≥ 1 laxative at least once weekly. Subjects on a stable laxative regimen at Screening were to remain on that regimen throughout the study. Any laxative use other than those designated as the subject's stable laxative regimen was considered rescue medication.

Regardless of being on a stable laxative regimen at baseline, if a subject had not had a BM for more than 72 hours at any point during the Screening or Treatment Periods, a rescue laxative (different from the subject's regular regimen for patients on a regular laxative regimen) was allowed. Subjects on stable laxatives at Screening were supposed to re-establish their baseline regimen as soon as possible following rescue medication use.

Randomization of subjects was not stratified by baseline laxative use. However, the proportion of subjects on a baseline stable laxative regimen was similar between groups. A total of 831 subjects (67.0 %) in the ITT population [411 in the naldemedine group (66.2 %) and 420 in the placebo group (67.7%)] were on a stable baseline laxative regimen. For both treatment arms, mean number of laxatives was 1.3 medications per subject, and median numbers of laxatives was 1.0 (range 1 to 4) medications. The types of laxatives in subjects' baseline regimens were generally similar between treatment arms (see Table 51 and Table 52). In both arms, stimulant laxatives were the most frequent class of laxatives used by subjects on stable regimens at baseline. Use of osmotic laxatives was somewhat higher in the naldemedine arm.

Among subjects in the higher opioid dose group (i.e., >100 mg), 72.6% of subjects were on maintenance laxatives at baseline (328/452), compared to 63.8% of subjects in the lower opioid dose group (i.e., 30-100 mg; 503/789). In the higher dose group 73.3% of the naldemedine arm and 71.8% of the placebo arm were taking maintenance laxatives, vs. 62.1% and 65.5% of the naldemedine and placebo arms of the lower dose group, respectively.

Table 52: Laxative Medications in Stable Regimens of Subjects with Baseline Laxative Use

	Naldemedine (N=621)	Placebo (N=620)
Any Laxative	411 (66.2)	420 (67.7)
Bisacodyl	184 (29.6)	205 (33.1)
Docusate	91 (14.7)	83 (13.9)
Polyethylene Glycol 3350	85 (13.7)	71 (11.5)
Sennosides	50 (8.1)	56 (9.0)
Magnesium-Based Laxatives	25 (4.0)	33 (5.3)
Fleet Enema	29 (4.7)	25 (4.0)

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Bulk Laxatives (Fiber)	22 (3.5)	14 (2.3)
Lactulose	16 (2.6)	12 (1.9)
Glycerin Suppository	11 (1.8)	12 (1.9)
Sodium Picosulfate	7 (1.1)	6 (1.0)
Stool Softeners NOS	0	6 (1.0)
Saline Enemas (exc phosphate)	3 (0.5)	2 (0.3)
Enemas NOS	1 (0.2)	3 (0.5)
Mineral Oil	1 (0.2)	1 (0.2)
Potassium Tartrate Suppository	2 (0.3)	0
Oral Laxative NOS	0	2 (0.3)
Sorbitol	1 (0.2)	0

(Source: Reviewer's table)

Abbreviations used in table: exc, except, NOS, not otherwise specified

Table 53: Classes of Laxatives in Stable Regimens of Subjects with Baseline Laxative Use

	Naldemedine (N=621)	Placebo (N=620)
Stimulant Laxatives	239 (38.5)	267 (43.0)
Osmotic Laxative, Oral	127 (20.5)	117 (18.9)
Stool Softeners	81 (13.0)	89 (14.4)
Enema-Osmotic	32 (5.2)	27 (4.4)
Bulk Laxatives (Fiber)	22 (3.5)	14 (2.3)
Suppository-Osmotic	13 (2.1)	12 (1.9)
Enemas NOS	1 (0.2)	3 (0.5)
Lubricants	1 (0.2)	1 (0.2)
Oral Laxatives NOS	0	1 (0.2)

(Source: Reviewer's table)

Abbreviations used in table: NOS, not otherwise specified

➤ Other Concomitant Medications

Non-opioid analgesic medications

In addition to opioids, 367 subjects (59%) in the naldemedine group and 403 subjects (65%) in the placebo group were receiving ≥ 1 non-opioid pain medication (Table 54). The most class of non-opioid analgesics in both groups were GABA analogues ($>1/3$ of both treatment arms), such as gabapentin and pregabalin, and non-steroidal anti-inflammatory drugs (NSAIDs). Use of NSAIDs, a class of medications with common adverse effect of constipation, was higher in the placebo group (36.0%, vs. 29.6% in the naldemedine arm).

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Table 54: Non-Opioid Analgesics Used by Subjects in the ITT Population of Study V9235

Analgesic Drug Class	Naldemedine (N=621)	Placebo (N=620)
GABA analogues (e.g., gabapentin, pregabalin, topiramate)	220 (35.4)	226 (36.5)
Non-Steroidal Antiinflammatory Drugs	184 (29.6)	224 (36.0)
Anilides (e.g., acetaminophen)	86 (13.8)	82 (13.2)
Salicylic Acid And Derivatives	38 (6.1)	29 (4.7)
Cyclooxygenase (COX)-2 Inhibitors	18 (2.9)	22 (3.5)

(Source: reviewer's table)

Concomitant medications (excluding analgesics and laxatives)

Classes of medications used by $\geq 5\%$ of the ITT population in Study V9235 are shown in Table 54. The most frequently used classes of concomitant medications (excluding analgesics and laxatives) in both groups were centrally acting muscle relaxants and benzodiazepines.

The only classes of medications with $>4\%$ difference in rate of use between treatment arms were SSRIs and centrally acting muscle relaxants, both of which are known to be associated with treatment-related constipation. In both cases, frequency of use was lower in the naldemedine arm, compared to placebo (17.2% and 35.4% in the naldemedine arm vs. 22.4% and 39.4% in the placebo arm, for SSRIs and centrally acting muscle relaxants, respectively).

Table 55: Concomitant Medications (Except Analgesics and Laxatives) Used by $\geq 5\%$ of the ITT Population, Study V9235

Medication Class/Group	Naldemedine (N=621)	Placebo (N=620)
Muscle relaxants, Centrally Acting	219 (35.3)	244 (39.4)
Benzodiazepines	208 (33.5)	211 (34.0)
Proton Pump Inhibitors	191 (30.8)	201 (32.4)
HMG CoA Reductase Inhibitors	192 (30.9)	178 (28.7)
Systemic Antibiotics, Oral	158 (25.4)	169 (27.3)
ACE Inhibitors	152 (24.5)	141 (22.7)
Selective Serotonin Reuptake Inhibitors	107 (17.2)	139 (22.4)
Beta Blockers	125 (20.1)	107 (17.2)
Platelet Aggregation Inhibitors (Excl. Heparin)	108 (17.4)	120 (19.4)
Serotonin–Norepinephrine Reuptake Inhibitors	104 (16.7)	108 (17.4)
Inhaled Beta-2-Adrenoreceptor Agonists	109 (17.6)	99 (16.0)
Thyroid Hormone	96 (15.5)	105 (16.9)
Blood Glucose Lowering Drugs (except Insulin)	90 (14.5)	111 (17.9)
Systemic Antihistamines	92 (14.8)	98 (15.8)
Calcium Channel Blockers	100 (16.1)	87 (14.0)
Vitamin D And Analogues	81 (13.0)	96 (15.5)

Medication Class/Group	Naldemedine (N=621)	Placebo (N=620)
Thiazides	85 (13.7)	77 (12.4)
Multivitamins	76 (12.2)	80 (12.9)
Misc. Antidepressants (Trazodone and Remeron)	67 (10.8)	83 (13.4)
Sedative Hypnotic Sleep Agents	73 (11.8)	76 (12.2)
Systemic Corticosteroids	62 (10.0)	66 (10.6)
Inhaled Corticosteroids	63 (10.1)	64 (10.3)
Angiotensin II Antagonists	64 (10.3)	62 (10.0)
Monoamine Reuptake Inhibitors	62 (10.0)	64 (10.3)
Loop Diuretics	56 (9.0)	57 (9.2)
Topical Anesthetics (Anilides)	44 (7.1)	44 (7.1)
Fish Oil/Omega Fatty Acids	34 (5.5)	49 (7.9)
Psychostimulants/Centrally Acting Sympathomimetics	31 (5.0)	44 (7.1)
Potassium Supplements	38 (6.1)	36 (5.8)
Histamine-2-Receptor Antagonists	34 (5.5)	38 (6.1)
Bupropion	41 (6.6)	30 (4.8)
5-HT ₃ Receptor Antagonist Antiemetics	39 (6.3)	30 (4.8)
Insulin	41 (6.6)	26 (4.2)
Estrogens	29 (4.7)	38 (6.1)
Alpha-Adrenergic Antagonists	36 (5.8)	30 (4.8)
Intranasal Corticosteroids	36 (5.8)	29 (4.7)
Triptans (Selective Serotonin Agonists)	38 (6.1)	29 (4.7)

(Source: Reviewer's table)

➤ Medical history

The sources of non-cancer pain reported by ≥1% of the ITT population in Study V9235 are shown in Table 56, and the most frequently reported medical history (reported by ≥10% of subjects) is shown in Table 57.

Consistent with the study populations in Studies V9231 and V9232, back pain was, by far, the most common source of non-cancer pain in both groups, and was also the most common medical condition reported overall. The only clinically relevant differences between treatment arms are a higher rate of hypertension and dyslipidemia in the placebo arm [differences (naldemedine-placebo) of -2.7% and -4.4%, respectively]. The magnitude of these differences is relatively small; however, it is notable that these risk factors for MACE were more prevalent in the placebo arm of this long-term safety study. Both groups had similar percentages of subjects with diabetes mellitus.

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Table 56: Sources of Non-Cancer Pain in ≥1% of the ITT Population, Study V9235

	Naldemedine (N=621)	Placebo (N=620)	Overall (N=1241)
Back Pain	345 (55.6)	375 (60.5)	720 (58.0)
Osteoarthritis	60 (9.7)	58 (9.3)	118 (9.5)
Neck Pain	48 (7.7)	53 (8.5)	101 (8.1)
Arthralgia	45 (7.2)	43 (6.9)	88 (7.1)
Pain	41 (6.6)	42 (6.8)	83 (6.7)
Fibromyalgia	33 (5.3)	33 (5.3)	66 (5.3)
Intervertebral Disc Compression/Degeneration	28 (4.5)	28 (4.5)	56 (4.5)
Spinal Osteoarthritis/Spondylolysis	18 (2.9)	22 (3.5)	40 (3.2)
Pain In Extremity	20 (3.2)	15 (2.4)	35 (2.8)
Intervertebral Disc Displacement/Protrusion	20 (3.2)	12 (1.9)	32 (2.6)
Musculoskeletal Pain	15 (2.4)	14 (2.3)	29 (2.3)
Spinal Stenosis	10 (1.6)	10 (1.6)	20 (1.6)
Arthritis/Arthropathy	10 (1.6)	10 (1.6)	20 (1.6)
Rheumatoid Arthritis	9 (1.4)	10 (1.6)	19 (1.5)
Headache/Migraine	12 (1.9)	6 (1.0)	18 (1.5)

(Source: Reviewer's table)

Table 57: Medical Conditions Reported in ≥10% of Subjects in the ITT Population, Study V9235

	Naldemedine (N=621)	Placebo (N=620)	Overall (N=1241)
Back Pain	400 (64.4)	419 (67.6)	819 (66.0)
Hypertension	302 (48.6)	318 (51.3)	620 (50.0)
Depression	261 (42.0)	274 (44.2)	535 (43.1)
Dyslipidemia	241 (38.8)	268 (43.2)	509 (41.0)
Anxiety/Anxiety Disorder	221 (35.6)	230 (37.1)	451 (36.3)
Osteoarthritis	203 (32.7)	214 (34.5)	417 (33.6)
Insomnia	201 (32.4)	214 (34.5)	415 (33.4)
Gastroesophageal Reflux Disease	203 (32.7)	212 (34.2)	415 (33.4)
Menopause/Postmenopause	163 (26.2)	164 (26.5)	327 (26.3)
Headache/Migraine	155 (25.0)	172 (27.7)	327 (26.3)
Hysterectomy	144 (23.8)	146 (23.5)	290 (23.4)
Drug Hypersensitivity	132 (23.2)	132 (21.3)	264 (21.3)
Diabetes Mellitus	120 (19.3)	121 (19.5)	241 (19.4)
Arthralgia	130 (20.9)	98 (15.8)	228 (18.4)
Intervertebral Disc Compression/Degeneration	103 (16.6)	108 (17.4)	211 (17.0)
Intervertebral Disc Displacement/Protrusion	114 (18.4)	93 (15.0)	207 (16.7)
Neck Pain	96 (15.5)	103 (16.6)	199 (16.0)
Spinal Osteoarthritis/Spondylolysis	98 (15.8)	99 (16.0)	197 (15.9)
Asthma/Bronchospasm	96 (15.5)	100 (16.1)	196 (15.8)
Obesity	93 (15.0)	96 (15.5)	189 (15.2)

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	Naldemedine (N=621)	Placebo (N=620)	Overall (N=1241)
Hypothyroidism	87 (14.0)	99 (16.0)	186 (15.0)
Seasonal Allergy	86 (13.8)	93 (15.0)	179 (14.4)
Spinal Fusion/Surgery	96 (15.5)	79 (12.7)	175 (14.1)
Muscle Spasms	74 (11.9)	99 (16.0)	173 (13.9)
Fibromyalgia	80 (12.9)	88 (14.2)	168 (13.5)
Cholecystectomy	81 (13.0)	77 (12.4)	158 (12.7)
Tubal ligation	68 (11.0)	80 (12.9)	148 (11.9)
Pain	69 (11.1)	74 (11.9)	143 (11.5)
Peripheral Neuropathy	71 (11.4)	61 (9.8)	132 (10.6)
Chronic Obstructive Pulmonary Disease	68 (11.0)	56 (9.0)	124 (10.0)

(Source: Reviewer's table)

Efficacy Results – Primary Endpoint

There was no primary efficacy endpoint in study V9235.

Efficacy Results- Secondary and Exploratory Endpoints

Laxative Use- Concomitant and Rescue Medications

Of the 411 subjects in the naldemedine group on a laxative regimen at baseline, 314 subjects (76.4%) maintained a stable concomitant laxative regimen during study participation, representing 50.6% of the entire naldemedine treatment arm. In the placebo arm, 336/420 (80.0%) of the subjects on laxatives at baseline maintained their stable regimen for the duration of study participation (54.2% of the treatment arm).

At the time of treatment completion or study termination, 40/411 (9.7%) subjects in the naldemedine arm and 25/420 (5.9%) subjects in the placebo arm with a baseline maintenance laxative regimen no longer had any ongoing laxative medications.

Rescue laxative use during the study treatment period was reported in 70 subjects in the naldemedine arm (11.3%) vs. 79 subjects in the placebo arm (12.7%). In the naldemedine arm, rescue laxative use occurred in 53/411 of subjects (12.9%) on a stable laxative regimen at baseline vs. 17/210 of subjects (8.1%) without concomitant maintenance laxative use. In the placebo arm, the rate of rescue laxative use was more similar between subjects with and without baseline concomitant laxative regimens, i.e., 54/420 (12.9%) and 25/200 (12.5%), respectively.

Fourteen subjects without laxative use at baseline (5 in the naldemedine arm and 9 in the placebo arm) had ≥ 1 ongoing concomitant laxative medication at the time of study completion/termination.

Table 58: Applicant’s Analysis Subgroups Based on Laxative Use

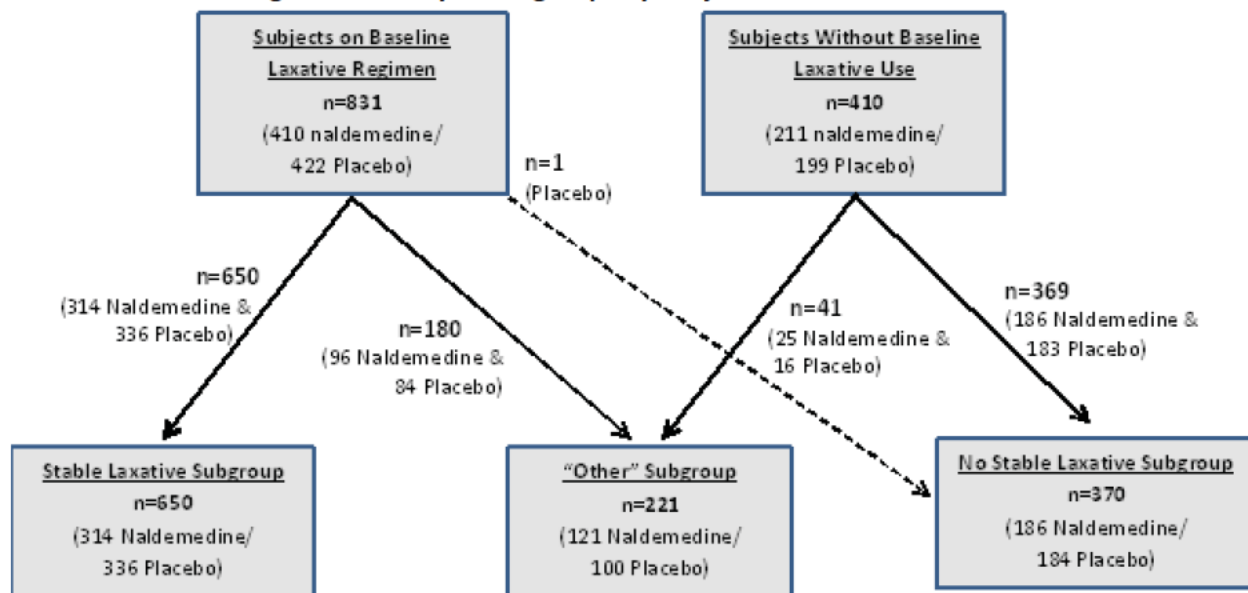
Analysis Subgroup	Subgroup Definition	Number of Subjects (%)	
		Naldemedine	Placebo
Subjects not on stable laxatives	Subjects who did not have laxative use reported or received only rescue	186 (30.0)	184 (29.7)
Subjects on stable laxatives	Subjects who had any stable laxative use reported (≥1 laxative)	314 (50.6)	336 (54.2)
Other subjects	Subjects who do not meet criteria for either of the other subgroups	121 (19.5)	100 (16.1)

(Source: Applicant’s Table S1 “Number of Subjects Meeting Each Criterion of Laxative Use Reported from 28 Days Prior to Screening to Last Dose of Study Drug – Intent-to-Treat Population”, Clinical Study Report: 1326V9235, page 8/2796)

Analysis Subgroups by Baseline Laxative Use

As discussed previously, the analysis subgroups defined by the Applicant are based on a combination of baseline and outcome characteristics. In addition, inconsistencies were identified in the classification of study subjects based on laxative use at baseline and during study participation. The distribution of these subjects based on baseline laxative use is shown in Figure 20.

Figure 19: Laxative Use During V9235: Analysis Subgroups by Subjects’ Baseline Laxative Use



Rescue Laxative Use

The proportion of subjects in the ITT population with rescue laxative use during Study V9235 was 11.3% (70/621) in naldemedine arm, compared to 12.7% (79/620) in the placebo arm, and the difference between groups (1.4%) was not statistically significant.

Table 59: Rescue Laxative Use by Analysis Subgroup and Baseline Laxative Use

	Naldemedine N=621	Placebo N=620	Overall (N=1241)
All	70 (11.3)	79 (12.7)	149 (12.0)
Stable laxative subgroup	23/314 (7.3)	41/336 (12.2)	64/650 (9.8)
No stable laxative subgroup	12/186 (6.5)	22/184 (12.0)	34/370 (9.2)
Other	35/121 (28.9)	16/100 (16.0)	51/221 (23.1)
Baseline laxative regimen	53/410 (12.9)	54/421 (12.8)	107/831 (12.9)
No baseline laxative use	17/211 (8.1)	25/199 (12.6)	42/410 (10.2)

(Source: Reviewer's table)

In both the stable laxative and no stable laxative subgroups, the proportion of subjects with rescue laxative use was higher in placebo arm, with p-values of 0.037 and 0.067, respectively. These data are misleading and provide an overestimate of the actual treatment effect on this outcome variable, and thus, should be used to conclude that naldemedine treatment is associated with a lower rescue laxative requirement, irrespective of concomitant maintenance laxative use. In the "other" subgroup, which consists of subjects with maintenance laxative usage that varied during study participation (i.e., increased, decreased, or discontinued all together), rescue laxative use was higher in the naldemedine arm.

Results of these subgroup analyses, as well as those for other efficacy variables, need to be interpreted with caution because they are based on post-hoc definitions that are not defined according to baseline characteristics. The Applicant's method of subgroup division inappropriately excludes meaningful subjects from their baseline categories (e.g., subjects without maintenance laxative use at baseline that required initiation of a maintenance laxative regimen during study participation) and creates a new category without definable baseline or outcome characteristics. Therefore, results for individual subgroups are not interpretable and are only useful when assessed in the context of results for the overall population.

When rescue laxative use is analyzed based on subjects' baseline laxative use, a treatment difference is only observed for the subjects' without established laxative regimens at baseline. Although these subgroup results are likely less biased by the post-hoc nature of the analyses

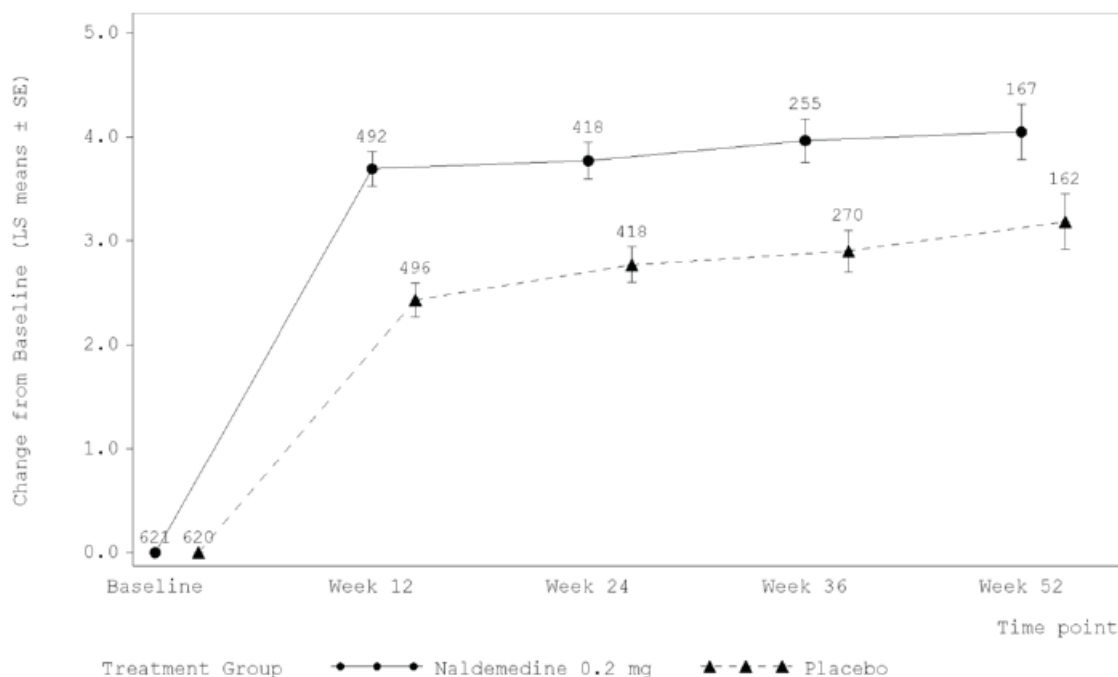
than those conducted by the Applicant, the interpretability of these data are limited by the loose criteria used to define baseline laxative use and lack of standardized procedures for concomitant laxative use.

Change in Weekly BM Frequency from Baseline

At 4 selected time points during the Treatment Period (Weeks 12, 24, 36, and 52), change in BM frequency per week from baseline was assessed using data from the Bowel Habits paper diary completed for the week prior to the specified time point. Frequency of BMs per week was calculated as the weekly average of observations in 7 days prior to each visit. At the time of data cutoff for the Core Period, all ongoing subjects had completed >24 weeks of treatment. Therefore, efficacy analyses for Weeks 12 and 24 include data for the full ITT population, while Week 36 and 52 efficacy analyses were performed using incomplete datasets, consisting of 37% fewer subjects for the Week 36 assessment and 61% fewer subjects for the Week 52 assessment, compared to the Week 24 assessment. The numbers of subjects in each treatment arm with available efficacy data at each time are shown in the figure.

Note: The Applicant did not assess SBM frequency during study treatment, only BM frequency. Therefore, these data do not account for rescue medication use.

Figure 20: Change in the Frequency of Bowel Movements per Week from Baseline to Each Visit Assessed (Least-Squares Mean $\pm$ Standard Error) – Intent-to-Treat Population, Core Period Dataset



(Source: Applicant’s Figure 11-1, “Change in the Frequency of Bowel Movements per Week from Baseline to Each Visit Assessed (Least-Squares Mean $\pm$ Standard Error) – Intent-to-Treat Population”, page 87/2796

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Table 60: Repeated Measures Analysis of Change in the Frequency of Bowel Movements per Week from Baseline – Study V9235 Intent-to-Treat Population, Core Period Dataset

Study Visit (Analysis Time Point)	LS Mean (SE) for Treatment Arm		Difference of LS Mean (95% CI)	P-value (Nominal)
	Naldemedine	Placebo		
Visit 6 (Week 12)	3.69 (0.163)	2.43 (0.163)	1.26 (0.82, 1.71)	<0.0001
Visit 8 (Week 24)	3.77 (0.173)	2.77 (0.173)	1.00 (0.53, 1.48)	<0.0001
Visit 10 (Week 36)	3.97 (0.209)	2.90 (0.205)	1.06 (0.50, 1.63)	0.0002
Visit 13 (Week 52)	4.05 (0.266)	3.18 (0.269)	0.87 (0.13, 1.60)	0.0214

(Source: Adapted from Applicant’s Table 11-3, Clinical Study Report: 1326V9235, page 86/2796)

Similar to the rescue laxative data, analyses of BM frequency based on the Applicant’s laxative subgroup definitions are difficult to interpret. In addition, the interpretability of BM frequency assessments are also impacted by the amount of missing data at Weeks 36 and 52 due to the data cutoff of the Core Period Data Set. For these reasons, subgroup analyses of BM frequency based on concomitant laxative use have not been included in this review.

Following the completion of Study V9235, the Applicant submitted updated datasets of BM frequency that included data accrued during the Supplemental Period. These include additional efficacy data for 232 subjects at Week 36 (total 757 subjects; vs. 525 subjects in Core Dataset analyses) and 373 subjects at Week 52 (total 702 subjects; vs. 329 subjects in Core Dataset analyses).

Analyses of mean changes in weekly BM frequency for the full study population (Core and Supplemental data) are shown in Table 61. With the full datasets, the difference between group means was lower at Week 36 and slightly higher at Week 52, but p-values were lower with the larger study population. (Note: formal efficacy analyses of the updated datasets were not performed by the Applicant.)

Similar to findings in the pivotal studies, a substantial placebo effect was also observed in Study V9235. Assessment of treatment effect was also more challenging in this study because of highly variable concurrent laxative use and incomplete rescue laxative data. Nevertheless, the observed treatment effect in the naldemedine arm (i.e., increase in BM frequency from baseline) was similar at all timepoints between Weeks 12 to 52 (Figure 22), providing evidence of sustained treatment response over time.

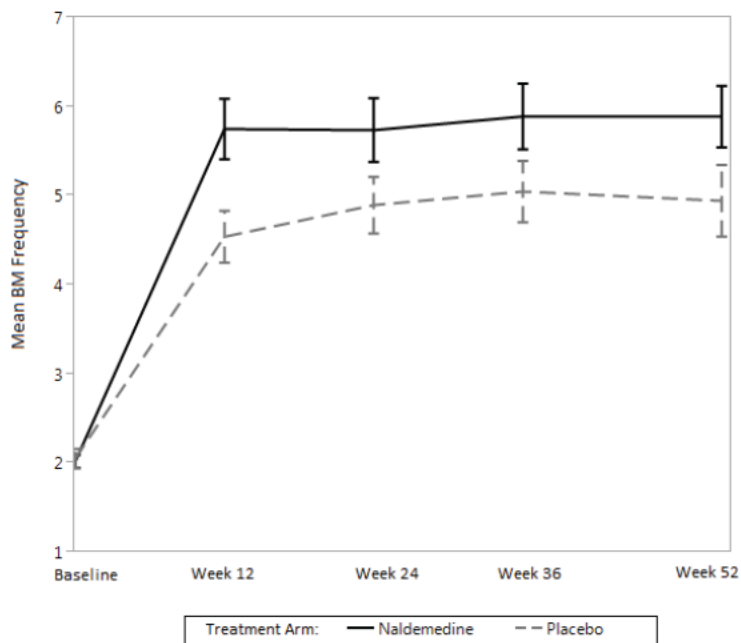
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Table 61: Change in Weekly BM Frequency from Baseline [Mean ($\pm$ SD)] at Weeks 12, 24, 36, and 52 for the Entire ITT Population of Study V9235 (Core and Supplemental Datasets)

Study Visit (Analysis Time Point)	Mean (SD)		Difference of Means	P-value
	Naldemedine	Placebo		
Visit 6 (Week 12)	3.77 ($\pm$ 3.85)	2.47 ($\pm$ 3.32)	1.30	<0.0001
Visit 8 (Week 24)	3.75 ($\pm$ 3.76)	2.87 ($\pm$ 3.36)	0.88	0.0004
Visit 10 (Week 36)	3.90 ($\pm$ 3.69)	3.02 ($\pm$ 3.48)	0.88	0.0007
Visit 13 (Week 52)	3.89 ($\pm$ 3.35)	2.97 ($\pm$ 3.81)	0.92	0.0007

(Source: Reviewer's table using analysis datasets from submission to NDA 208854/SN 0009, dated 6/22/2016)

Figure 21: Mean ($\pm$ 95% CI) Weekly BM Frequency over Time for the full ITT study Population (Core and Supplemental datasets) of V9235 (N=1241)

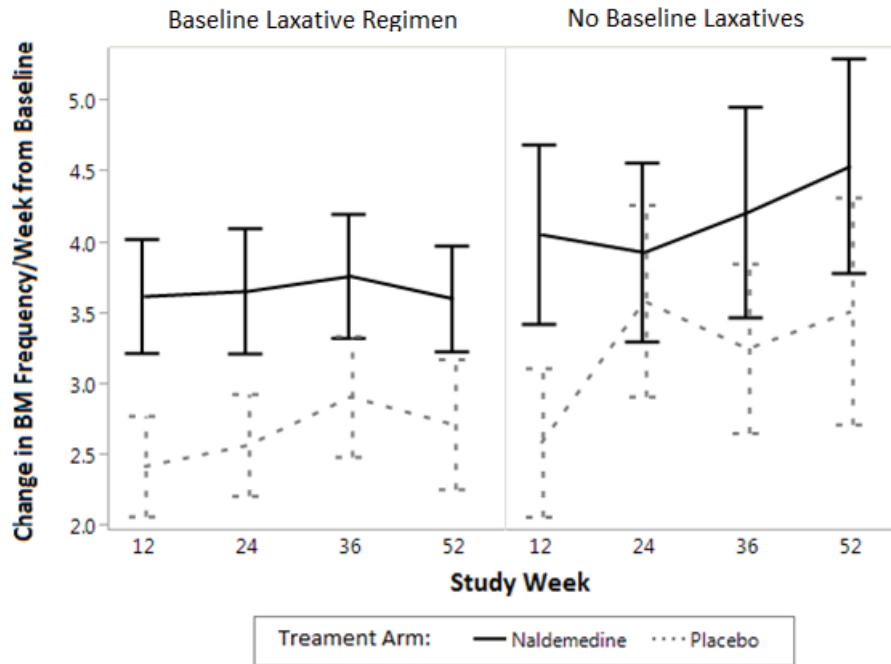


(Source: Reviewer's figure)

Subgroup analyses based on subjects' baseline laxative use are of limited usefulness due to issues related to study design and relatively small size of the subgroup without baseline laxative use. Mean ($\pm$ 95% CI) changes in weekly BM frequency over time for the 2 baseline laxative subgroups (i.e., established stable laxative regimen vs. no laxative use) are shown in Figure 23

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Figure 22: Change in Mean ($\pm$ 95% CI) Weekly BM Frequency over Time By Baseline Laxative Use for the full ITT study Population (Core and Supplemental datasets) of V9235 (N=1241)



(Source: Reviewer's figure)

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy across Trials

7.1.1. Subject Disposition

Figure 13 shows the subject disposition across the 3 phase 3 placebo-controlled naldemedine clinical trial for this application.

Study discontinuations for the 3 Phase 3, placebo-controlled trials are summarized in Table 62.

Table 62: Subject Discontinuations in Phase 3, Placebo-Controlled Clinical Trials

Category	Reason/Type	12-week (Studies V9231 & V9232)		52-week (Study V9235)		Total	
		Naldemedine (N=549)	Placebo (N=550)	Naldemedine (N=623)	Placebo (N=623)	Naldemedine (N=1170)	Placebo (N=1166)
Any	Any	79	77	208	207	287	284
Withdrawal by Subject	Any	31	41	61	72	92	113
	Study requirements	13	7	11	11	24	18
	Lack of Efficacy	4	15	4	15	8	30
	Distance/transportation	3	5	13	12	16	17
	Personal/family	4	3	8	9	12	12
	Opioid discontinuation/ dosage decrease	0	1	3	7	3	8
	Surgery/medical condition	1	3	5	2	6	5
	Prohibited med/trial	0	1	0	4	0	5
	Recommendation by other health provider	0	1	2	3	2	4
	Detox admission	0	0	1	0	1	0
Reason not specified	6	5	14	9	20	14	
Adverse Event	Any	32	17	49	40	81	57
	GI symptoms	16	9	22	8	36	16
	Opioid Withdrawal	4	1	4	4	8	5
	Pain	2	0	4	4	6	4
	Death	1	0	3	4	4	4
Other	9	7	16	20	25	26	
Lost to follow-up	All	9	10	53	40	62	50

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Category	Reason/Type	12-week (Studies V9231 & V9232)		52-week (Study V9235)		Total	
		Naldemedine (N=549)	Placebo (N=550)	Naldemedine (N=623)	Placebo (N=623)	Naldemedine (N=1170)	Placebo (N=1166)
Protocol Violation	Any	7	8	35	41	42	49
	Study Noncompliance	4	5	11	12	15	17
	Prohibited treatment	0	1	6	9	6	10
	Prohibited GI history (Bariatric surgery/IBS)	0	0	3	5	3	5
	Duplicate subject	0	0	4	3	4	3
	Drug abuse/Illicit use	0	0	1	3	1	3
	Opioids stopped/decreased	2	0	8	4	10	4
	Other drug trial	0	0	2	1	2	1
	Pregnancy	0	0	0	1	0	1
	Other exclusion criteria	0	1	0	2	0	3
Other	Randomization error	1	1	0	0	0	2
	Any	0	1	10	14	10	15
	IMP unblinding	0	0	3	7	3	7
	Site Closure	0	0	4	5	4	5
	PI discretion	0	0	3	2	2	3
	Incarceration	0	1	0	0	1	0

(Source:

Abbreviations used in table: IMP, ; GI AE- predominantly GI symptoms

More detailed discontinuations due to AEs in Section 8.4.3.

Not treated

Other: hep C (n=1), cancer (n=1), opioid drug allergy (n=1)

7.1.2. Primary Endpoints

For both efficacy clinical trials, Study V9231 and Study V9232, the proportion of SBM responders was higher in the naldemedine arm compared to the placebo arm, with statistically significant differences between treatment arms achieved in both trials (p-values 0.0020 and <0.0001, respectively). Of note, the absolute responder rates for individual treatment arms and the differences between groups (13.0% and 18.9%, respectively) are comparable to those observed in clinical trials for other PAMORAs.

(Note: Efficacy endpoints in Study V9235 were different than Studies V9231 and V9232.)

Table 63: Primary Efficacy Analysis in Pivotal Studies of Efficacy

Clinical Trial	Treatment Arm: Proportion of Responders, % (95% CI)		Difference of Proportions	
	Naldemedine (N=549)	Placebo (N=546)	% (95% CI)	<i>p-value</i>
Study V9231	47.6 (41.6, 53.7)	34.6 (28.9, 40.5)	13.0 (4.8, 21.3)	0.0020
Study V9232	52.5 (46.5, 58.6)	33.6 (28.0, 39.5)	18.9 (10.8, 27.0)	<0.0001

(Source: Reviewer's table)

Primary analyses for the primary endpoint of Study V921 and Study V9232 used a pro-rated value for weekly SBM frequency that used a correction factor for the number of days with completed eDiary entries for the week, provided that eDiary data were available for ≥4 days of that week. This method for handling missing eDiary data is based on an assumption that the likelihood of an SBM event is the same on days with and without completed eDiary entries. However, the principle of response bias would suggest that subjects would be more likely to complete eDiary entries on days with events to report (e.g., bowel movement event, use of rescue medication), which could result in an inflated difference between treatment groups.

Among the sensitivity analyses conducted for the primary endpoint to address potential effects of missing data on efficacy results was the “modified worst case”, which defined weekly SBM frequency as the observed number of SBMs in a week, rather than the pro-rated SBM frequency corrected for the number of days with completed eDiary entries, but still with minimum 4 days with eDiary data to be considered evaluable. This analysis method yielded similar results to the primary analysis (Table 24), indicating that missing eDiary entries had an insignificant impact on efficacy results.

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7.1.3. Secondary and Other Endpoints

In both trials, the results for the naldemedine group were statistically better than placebo for all 4 key secondary endpoints.

Pooled Secondary Endpoint Analyses

Pooled analyses of phase 3 clinical trial data (Study V9231 and V9232) for the 4 key secondary endpoints using the Applicant’s pre-specified statistical methodology are summarized in Table 63. As discussed in the reviews of the individual clinical trials in Section 6, the Applicant’s use of pro-rated BM event frequencies relies on mathematical correction for the number of days/week with completed diary entries, which is not considered appropriate by this reviewer due to the risk of introducing bias into the analyses in favor of the naldemedine treatment arm. This concern is supported by the comparison between analyses of adjusted and unadjusted data (Table 64), which shows the increase in frequency after adjustment was consistency disproportionately greater in the naldemedine group than the placebo group, suggesting a response bias in favor of the naldemedine group

Table 64: Pooled Secondary Endpoint Data for Studies V9231 and V9232, ITT Populations

Secondary Endpoint (Change in Frequency)	Treatment Arm, LS Mean (SE)		Difference of LS Mean Naldemedine-Placebo	
	Naldemedine (N=549)	Placebo (N=546)	n 95% CI	<i>p-value</i>
SBM/Week: Baseline to Last 2 Weeks	3.50 (0.130)	2.15 (0.129)	1.35 (0.99, 1.71)	<0.0001
SBM/Week: Baseline to Week 1	3.68 (0.136)	1.53 (0.135)	2.14 (1.77, 2.51)	<0.0001
CSBM/Week: Baseline to Last 2 Weeks	2.68 (0.119)	1.59 (0.119)	1.08 (0.76, 1.41)	<0.0001
SBM without Straining/week: Baseline to Last 2 Weeks	1.66 (0.108)	0.92 (0.107)	0.74 (0.44, 1.02)	<0.0001

(Source:

Abbreviations: CI, confidence interval; CSBM, complete spontaneous bowel movement; LS, least squares; SBM, spontaneous bowel movement

Table 65: Pooled Secondary Endpoint Adjusted and Unadjusted Data for Studies V9231 and V9232, ITT Population

Secondary Endpoint (Change in Frequency)	Frequency Calculation Method	Treatment Arm, LS Mean		Δ, n	Diff' ADjh and unadj
		Naldemedine (N=549)	Placebo (N=546)		
SBM/Week: Baseline to Last 2 Weeks	Adjusted	3.50	2.15	1.35	0.21
	Unadjusted	3.20	2.06	1.14	
SBM/Week: Baseline to Week 1	Adjusted	3.68	1.53	2.14	0.11
	Unadjusted	3.50	1.47	2.03	
CSBM/Week: Baseline to Last 2 Weeks	Adjusted	2.68	1.59	1.08	0.17
	Unadjusted	2.47	1.56	0.91	
SBM without Straining/Week: Baseline to Last 2 Weeks	Adjusted	1.66	0.92	0.74	0.09
	Unadjusted	1.56	0.91	0.65	

(Source: Reviewer's table)

Although results of secondary endpoints achieved statistical significance, calculated differences between group means for the differences are not inherently clinically meaningful, and the minimum difference between group means for each of these secondary endpoints that would represent a clinically meaningful treatment effect is not known.

In an effort to determine the clinical meaningfulness of secondary endpoint data, the Agency requested that the Applicant construct cumulative distribution function (CDF) plots of subject global satisfaction (SGS) scores and secondary endpoint data (figures located in Appendix , Section 13.4). These analyses demonstrated a positive correlation between increase in each of the BM events and higher SGS score, suggesting clinically meaningful treatment benefit. However, the SGS questionnaire was not considered adequately worded to elicit responses regarding satisfaction specifically related to symptoms of constipation.

7.1.1. Dose and Dose-Response

Naldemedine 0.2 mg once daily was the only dose evaluated in the naldemedine phase 3 clinical trial program.

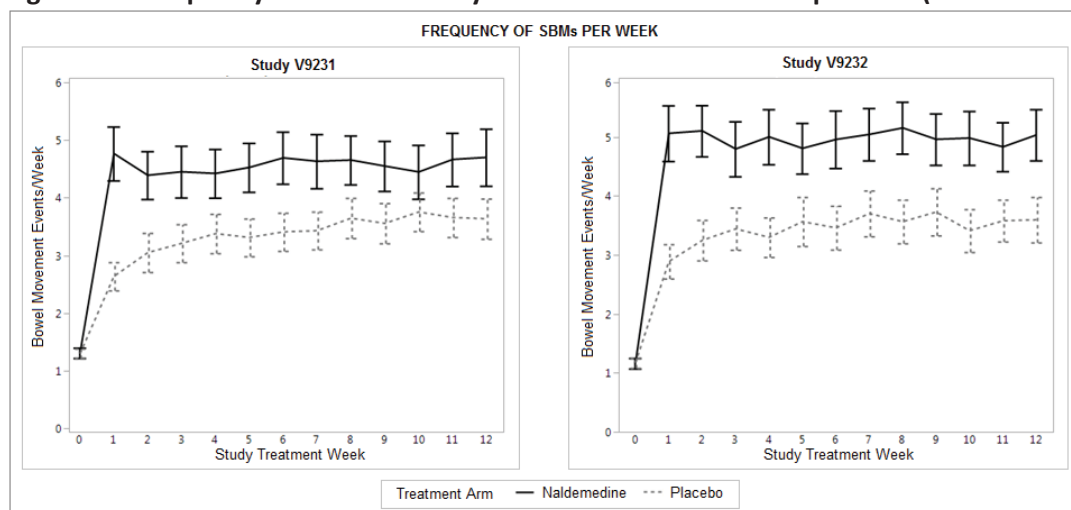
7.1.2. Dose/Dose Response

Only 1 naldemedine dosage (0.2 mg once daily) was evaluated in controlled phase 3 clinical trials, including Study V9231. Therefore, analyses of dose-response are limited to the phase 2 clinical trial (see Section 5.5.2).

Onset, Duration, and Durability of Efficacy Effects

The responder definition for primary efficacy analyses includes a specific criterion (i.e., weekly response for 3 of the last 4 weeks of the treatment period) to incorporate a requirement for durability of response. In addition, onset and durability of efficacy is shown by analysis of weekly SBM over time, which demonstrates response starting during Week 1, which was maintained throughout the study treatment period. (Figure 24) Similar maintenance of response was observed for other evaluated BM events. Figure 25 shows the frequency of SBM/week with BSS score of 3 or 4 (desirable stool consistency).

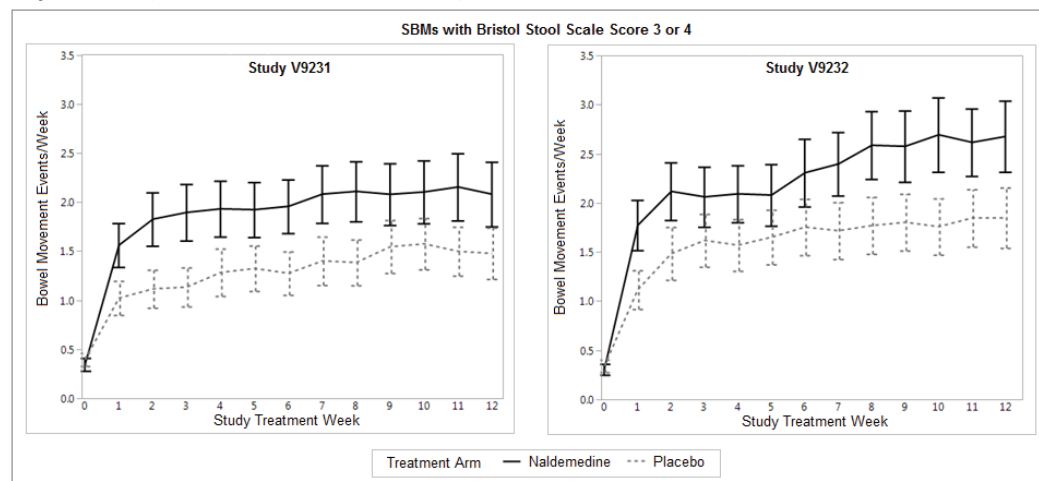
Figure 23: Frequency of SBM Per Study Week over Time for ITT Population (Studies V9231 and V9232)



(Source: Reviewer's figure)

Figure 24: Frequency of SBM with Bristol Stool Scale 3 or 4 Per Study Week over Time for ITT Population (Studies V9231 and V9232)

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(Source: Reviewer's figure)

7.1.3. Subpopulations

Subpopulation analyses were conducted for the primary endpoint of the 2 main efficacy trials (Study V9231 and V9232). Overall, findings were consistent among different subgroups in both studies, demonstrating higher response rate in subjects treated with naldemedine (vs. placebo). The only exception was the black racial subgroup in study V9232. However, the racial distribution of all studies was disproportionately white (approximately 80% of the pooled ITT population), and the black racial subgroup comprised only 18.5% and 15.5% of the ITT population of Study V9231 and V9232, respectively.

The only notable demographic subgroup analysis was age, which showed higher response rate among naldemedine-treated subjects aged <65, compared to naldemedine-treated subjects ≥65 years old. However, treatment effect (i.e., difference in proportion of responders between the naldemedine and placebo arms) was similar between age groups. The lower response rate in subjects aged ≥65 years old, regardless of treatment arm may be attributable to effects of age-related idiopathic constipation.

Table 66: Demographic Subgroup Analyses of the Primary Endpoint for the ITT Population of Studies V9231 and V9232

	Study V9231		Study V9232	
	Naldemedine 0.2mg	Placebo	Naldemedine 0.2mg	Placebo
Gender				
Male	55.4% (62/112)	34.6% (36/104)	56.8% (63/111)	39.6% (42/106)
Female	42.2% (68/161)	34.5% (58/168)	49.7% (82/165)	29.8% (50/168)
Race				
Black	49.1% (26/53)	41.7% (20/48)	40.8% (20/49)	46.2% (18/39)
White	47.2 % (102/216)	33.2% (73/220)	54.5% (121/222)	31.3% (71/227)
Age				
< 65 years	48.7% (114/234)	35.6% (80/225)	50.9% (118/232)	31.4% (74/236)
≥ 65 years	41.0% (16/39)	29.8% (14/47)	61.4% (27/44)	47.4% (18/38)
Region				
US	45.2% (104/230)	34.9% (80/229)	53.9% (130/241)	32.6% (78/239)
Non-US	60.5% (26/43)	32.6% (14/43)	42.9% (15/35)	40.0% (14/35)

N=number of patients; SE=Standard Error

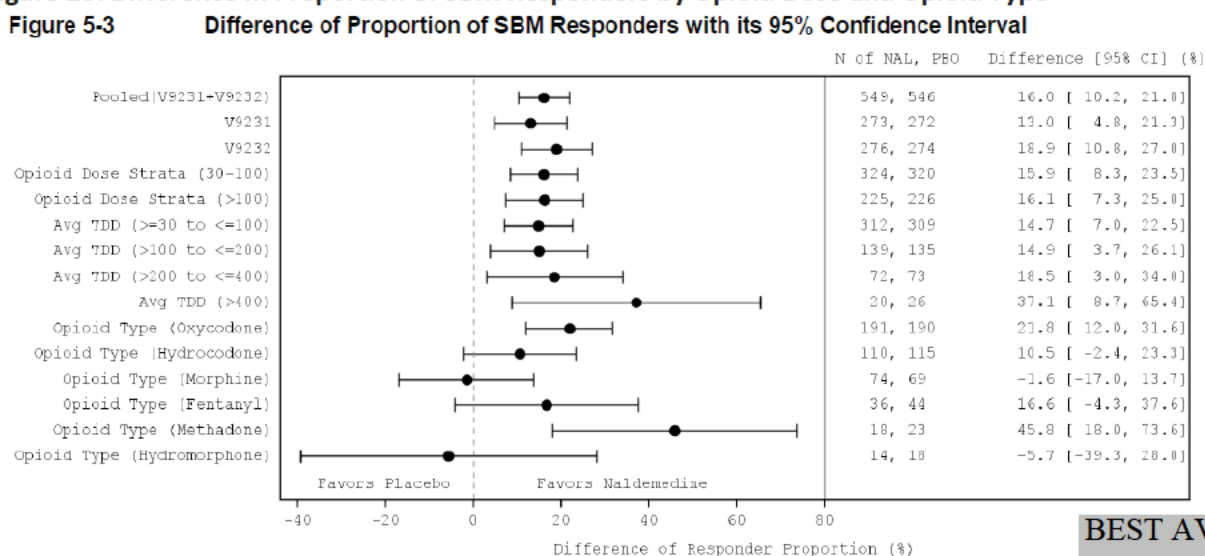
(Source: Statistical review, Table 13, entitled “Reviewer’s Subgroup Summary: Proportion of Responders by Gender, Race, Age, and Geographic Region Subgroups”, submitted by George Kordzakhia, Ph.D)

In addition, the Applicant conducted subgroup analyses based on opioid use. These results (Figure 26) demonstrate similar results for the 2 opioid dose strata. When analyzed by narrower ranges of opioid doses, results were generally similar across groups and comparable to pooled results, with the exception of subjects with baseline TDD of >400 mg morphine equivalents (the highest strata), which had a difference in response rate >2-fold higher than the pooled population and ~2-fold higher than the other subgroups. No trend was observed among the other subjects. Notably, the >400 mg dose group included far fewer patients than the other

subgroups, representing only 3.6% of the naldemedine group and 4.8% of the placebo group (4.2% of the total population).

Compared to opioid dose-based groups, greater variability in comparative response rates was observed among opioid medication types. However, these subsets were also generally smaller than the opioid dose groups. For the different opioid subtypes, the most notable differences were observed for the morphine and hydromorphone subgroups, who had treatment differences in response rate favoring placebo (Δ -5.7% and -1.6%, respectively), and the methadone subgroup, who had the largest observable treatment difference (Δ 45.8%). For the morphine and methadone subgroups, the 95% confidence intervals for the difference in proportions excluded the value for the pooled population (16%).

Figure 25: Difference in Proportion of SBM Responders by Opioid Dose and Opioid Type



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Source: Applicant's Figure 5-3, Integrated Summary of Efficacy, NDA 208854, Module 5.3.5.3)

8 Review of Safety

Safety Review Approach

The safety analysis dataset for this application consists of a pooled placebo-controlled safety population of randomized subjects who received at least 1 dose of study drug in the naldemedine clinical trial, focusing primarily on the data analyses conducted in the target (proposed) treatment population—i.e., patients with OIC and chronic, non-cancer pain—for which the majority of the safety data were obtained from 3 double-blind, placebo-controlled phase 3 trials, Studies V9231, V9232, and V9235. However, Study V9235 is the only one of these 3 trials with safety data in patients receiving extended study treatment (naldemedine or

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placebo).

While Studies V9231 and V9232 were replicate efficacy trials in which subjects received up to 12 weeks of study treatment, Study V9235 was a 52-week trial whose primary objective was to evaluate the long-term safety of naldemedine in patients with OIC and chronic, non-cancer pain. (Refer to Section 5 for discussion of each of the trial's design and conduct.) Safety data were analyzed for each individual trial's safety population. Because study procedures were the same for Studies V9231 and V9232, analyses of their pooled safety analysis populations were also performed, permitting a broader safety evaluation across the target treatment population. Safety data from other clinical trials (phase 1 trials in healthy individuals, phase 2 trials in patients with OIC and chronic, non-cancer pain, and all trials in patients with OIC and cancer-related pain) are considered supplementary, and in general, only notable findings are reported.

This review includes focused analyses performed to assess for 2 specific potential safety concerns—opiate withdrawal and major adverse cardiac events (MACE), both of which were identified based on findings from previous clinical trials of other PAMORAs.

Opioid withdrawal symptoms, which suggest the mu opioid antagonist effects in OIC may not be limited to peripheral receptors in all patients, have been noted in the review of safety data from OIC clinical trials. Therefore, in addition to assessment of AEs for evidence of opioid withdrawal, standard evaluation includes Opioid Withdrawal Scales, conducted at a frequency to provide clinically meaningful information. Also, because opioid withdrawal represents a constellation of relatively non-specific symptom, pre-defined adverse events potentially related to opioid withdrawal are needed, as well as use of a standardized MedRA Query (SMQ) of Drug Withdrawal Syndrome.

Unlike the risk of opiate withdrawal, the clinical significance of MACE and their relationship to study treatment observed in clinical trials of another PAMORA, Enetereg, have not been determined. The biological plausibility of these findings is substantial enough to support the safety concerns raised during this trial. However, it remains unclear whether this should be deemed a class-wide concern, or whether these data represent a true safety signal.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 2136 subjects were exposed to naldemedine (≥ 1 dose) throughout the entire naldemedine clinical development program, of which 1163 were patients with OIC and chronic, non-cancer pain enrolled in Phase 3 placebo-controlled clinical trials.

8.2.2. Adequacy of the safety database:

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As noted by the Applicant, the size of the naldemedine safety database and extent of exposure in the is similar to clinical development programs for other PAMORAs and follows the ICH guideline's general recommendation for long-term treatment of non-life-threatening conditions (i.e., 1500 subjects exposed in multiple dose studies, with 300-600 exposed for 6 months and 100 exposed for 1 year, at relevant doses). However, it is important to note that rare safety events often go undetected prior to approval because exposure to a drug during clinical trials is relatively small compared to the number of patients treated after approval. Therefore, larger safety databases would be required to quantify the rate of specific low-frequency AE prior to marketing approval.

Due to unresolved cardiovascular safety concerns identified based on Entereg clinical trial data, an advisory committee meeting (AADPAC) was held to in June 2014 to discuss whether pre-approval, prospective studies are needed to assess for risk of MACE for any or all of the PAMORAs being developed for treatment of OIC in non-cancer pain patients.

SUMMARY OF ADVISORY COMMITTEE RECOMMENDATIONS:

The gold standard for such assessments is a CVOT are resource intensive and may be impractical for OIC drug programs. Their feasibility is limited by the large sample size and long duration of exposure needed to observe a sufficient number of events to attain a desired level of statistical power, and draw meaningful conclusions on causality.

Alternative options to obtaining CV data using a combination of pre-approval and post-marketing observational data were discussed; taking into consideration causality is extremely difficult to establish without a concurrent control group, unless the events would be exceedingly rare in the patient population.

Following the AC meeting, the Applicant stated an intention to conduct a randomized (1:1), placebo-controlled safety trial in 1500-patients randomized 1:1 to receive naldemedine or placebo. Although the study was intended as a CVOT, no specific enrichment strategies were discussed.

During the EOP2 meeting, the sponsor proposed to change the primary endpoint of Study V9235 to the general safety of naldemedine and decrease the planned population to 1200 subjects. Because no formal calculations were used to determine sample size for this trial, this study was not designed to rule out a prespecified increase in CV risk with a cumulative exposure insufficient to observe a sufficient number of events to attain a desired level of statistical power (given background event rate).

By contrast, sample sizes for event-driven trials such as CVOTs are powered around the number of events and the amount of patient-years of exposure needed to observe these events. This is calculated based on a pre-specified risk margin (e.g. hazard ratio risk margin), an assumed true

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risk of the treatment related to the control, and the desired level of power (typically 90% for CVOTs).

Given the challenges of conducting formal CVOTs, the Division agreed to the proposed changes in the Study V9235 trial design. However, the Division cautioned the Applicant that drop-out rates in long-term trials for OIC have historically been ~30%, notably higher than the Applicant's predicted rate of 10%, and safety events might not be attributable to the assigned treatment if a large number of subjects discontinue treatment early in the study.

Although Study V9235 was not conducted as a formal CVOT, this study included pre-specified definitions of MACE, procedures to collect information relevant to the assessment of MACE events, and prospective, independent, external adjudication for all potential major adverse CV events (MACE), all in accordance with current Division recommendation for developing mu opioid receptor antagonists for OIC. Therefore, Study V9235 is the first long-term safety trial of a PAMORA that incorporated vigorous, comprehensive procedures for prospective and objective assessments for MACE and other class-wide safety concerns. However, it is important to note that even with a pre-specified plan for ascertainment of CV events, given the typically limited sample size and duration of the controlled studies, it may be difficult to make valid conclusions regarding the significance of rare events, even if numerical imbalances among treatment arms are observed.

Because pre-marketing trials are without prespecified features of a CVOT and are of a size that could detect only large increases in MACE risk, and then only if patients with higher cardiovascular risk were included, post-marketing observational studies would be needed to further quantify the potential risk of MACE associated with use of these drugs in real-world healthcare settings and with large numbers of patients, as communicated by most of the AADPAC members.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The quality of this submission was good, and the submission was well organized. The information in the submission provided all elements as agreed upon during the pre-NDA meeting, with the minor exception of the protocol deviations for Study V9235 and the need for minor data clarifications.

8.3.2. Categorization of Adverse Events

General

Adverse events were coded with MedDRA (Version 16.0) terms and then summarized by SOC and preferred term.

Treatment emergent adverse events (TEAEs) were defined as those that occurred after the initial dose of study drug up to 28 days after the final dose of study drug.

Causality: the relationship of the adverse event to the study drug was to be determined by the Investigator according to the following criteria

- Not related: The event could be clearly explained by a causative factor other than the study drug, or there was no reasonable temporal relationship between administration of the study drug and the occurrence of the adverse event
- Possibly related: Involvement of other causative factors than the study drug could be considered, but a causal relationship with the study drug could not be ruled out
- Probably related: Involvement of other causative factors than the study drug was unlikely
- Definitely related: There was a reasonable temporal relationship between administration of the study drug and occurrence of the adverse event, and there were no other causative factors other than the study drug that could explain the event

The severity of the adverse event was to be assessed by the Investigator according to the following definitions:

- Mild: The subject experienced awareness of symptoms but these were easily tolerated or managed without specific treatment
- Moderate: The subject experienced discomfort enough to cause interference with usual activity, and/or the condition required specific treatment
- Severe: The subject was incapacitated with inability to work or do usual activity, and/or the event required significant treatment measures

Abuse, Misuse, Overdose, and Medication Error

Immediate reporting using a Special Situation Report Form was required for identified cases of abuse, misuse, overdose, and medication error, defined as the following:

- Abuse: persistent or sporadic, intentional excessive use of an investigational product, which was accompanied by harmful physical or psychological effect
- Misuse: intentional and inappropriate use of an investigational product(s) other than as directed or indicated at any dose. Cases of subjects missing doses of investigational product were not considered reportable as misuse
- Overdose – Intentional or unintentional intake of a dose of investigational product(s) higher than the assigned dose in the protocol

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- Medication Error – Any unintended error in the prescribing, dispensing, or administration of an investigational product.

Adjudication of Major Cardiovascular Events

In Studies V9231, V9232 and V9235, blinded medical review and adjudication of all events known or suspected to be a MACE was performed by an external independent Cardiovascular Adjudication Committee (CAC) consisting of experienced cardiologists. The following procedures were implemented to optimize identification and review of all cardiovascular events:

- All treatment-emergent adverse events related to MACE were adjudicated by the CAC and were summarized by the following MACE type and treatment group: CV death, myocardial infarction, and cerebrovascular accident (stroke).
- Adjudication was also performed for cases of chest pain or other symptoms typical of acute coronary syndrome, including symptoms that may have overlapped with opioid withdrawal (ie, COWS, SOWS) with detailed documentation of the potential presence of opioid withdrawal symptoms (ie, COWS, SOWS) for each case
- Investigators were responsible for assessment of all CV-related events, with particular attention to MACE including CV death, myocardial infarction, and cerebrovascular accident.
- The Applicant specified a reporting requirement for any suspected CV events via electronic data capture (EDC) within 24 hours of awareness to ensure timely CAC adjudication. Investigators were required to collect documents related to the event (eg, ECGs, laboratory data, adverse event, SAE information, etc.) and assemble an event-specific package that was submitted to the CAC for review and adjudication. A checklist of expected documents for the type of event was provided to Investigators following EDC notification to assist with package completion.
- The Applicant and medical monitor conducted regular reviews of adverse events and SAEs to identify any additional CV-related safety events that may not have been reported by Investigators. For additional CV-related events identified as a result of the Applicant's review, Investigators were asked to provide detailed information for each event. The trial database was also periodically searched using Standard MedDRA Queries (Cardiac Arrhythmias SMQ, Cardiac Failure SMQ, Cardiomyopathy SMQ, Cerebrovascular disorders SMQ, Embolic and Thrombotic Events SMQ, Ischemic heart disease SMQ, Shock SMQ, and Torsade de pointes/QT prolongation SMQ) and any newly identified events were considered for adjudication.

8.3.3. Routine Clinical Tests

Standard Safety Assessments

Blood samples for chemistry and hematology and urine samples for urinalysis were to be collected at times indicated in Section 6.3.1. In addition, a separate Liver Event Form was provided for events which met the criteria prespecified in the protocol.

Other Safety Assessments: Tools Specific to this Application/Class of medications

Questionnaire Assessments for Opiate Withdrawal Signs and Symptoms

- Clinical Opiate Withdrawal Scale (COWS):
 - Completed by site personnel at study site
 - 11-item questionnaire
 - Total scores used to assess overall severity of withdrawal
 - (mild= 5 to 12; moderate= 13 to 24; moderately severe= 25 to 36; severe >36)
 - V9231 and V9232 The COWS assessment was to be performed at:
 - Visit 2 (Day 1) (at pre-dose and at 60, 90, 120 minutes post dose [$\pm$ 10 minutes])
 - Visit 3 (Week 1), Visit 4 (Week 2), Visit 5 (Week 4), Visit 6 (Week 8), and Visit 7 (Week 12) (or at Early Termination), at any time during the visit
 - If a COWS total score was $\geq$ 5 or indicated a worsening of withdrawal symptoms, the Investigator or designee was to complete a supplemental Elevated COWS Evaluation Form
 - Data analysis:
 - Summary statistics of the total COWS score (sum of scores on all items) and change from baseline to each scheduled visit were calculated by treatment group.
 - Plots of means of the absolute value (and their standard deviation) over time were presented by treatment group.
 - Analysis of COWS score were performed excluding abdominal pain
- Subjective Opiate Withdrawal Scale (SOWS):
 - Completed by
 - 16-item questionnaire, 5-point rating scale (0=not at all; 1=a little; 2=moderate; 3=quite a bit; and 4=extreme)
 - Used to identify subjects with possible opioid withdrawal
 - Scores do not correlate with specific levels of withdrawal
 - Useful to identify and track potential opioid withdrawal symptoms

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- If a SOWS assessment indicated worsening of withdrawal symptoms, the Investigator or designee completed a supplemental Elevated COWS Evaluation Form to further assess for opioid withdrawal and an unscheduled follow-up COWS assessment was administered as deemed necessary by the Investigator
- The SOWS assessment was to be performed at:
 - Visit 2 (Day 1) (at pre-dose and at 1 hour post dose [$\pm$ 10 minutes])
 - Between Visit 2 (Day 1) and Visit 4 (Week 2) (ie, first 14 days on study drug) SOWS was to be performed daily by the subject. Subjects performed the SOWS approximately 1 hour after dosing study drug
 - Visit 4 (Week 2), Visit 5 (Week 4), Visit 6 (Week 8), and Visit 7 (Week 12) or Early Termination, and at any time during the visit
- Means of the total SOWS score were calculated for each week using the formula: (Total of week's SOWS scores) / (Number of days of observation for the week)
 - Summary statistics of the total SOWS score and change from baseline to each scheduled visit were calculated by treatment group.
 - If multiple records were available in a day, the highest total score was used
 - Analysis of SOWS score with and without abdominal pain questions

Pain Assessments

- 11-point Numeric Rating Scale (NRS): measurement of severity of pain
 - Completed by
 - Rating scale: 0 to 10 (0=no pain and 10=worst possible pain)
 - (0, no pain; 1 to 3, mild pain; 4 to 6, moderate pain; and 7 to 10, severe pain)
 - Studies V9231 and V9232: Completed at the study site at every visit Visit 2 (Day 1) and through Visit 7 (Week 12) or Early Termination
 - Data analyses:
 - Summary statistics of the NRS score for pain evaluation and change from baseline to each scheduled visit were calculated by treatment group.
 - Plots of means (standard deviation) over time by treatment group
 - Summary of outliers (number and percentage) by treatment group
- Opioid Analgesics: assessment of pain based on change in average total daily and weekly dose of opioids from baseline

Standard Safety Assessments

Blood samples for chemistry and hematology and urine samples for urinalysis were to be collected at times indicated in Section 6.3.1. In addition, a separate Liver Event Form was provided for events which met the criteria prespecified in the protocol.

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Other Safety Assessments: Tools Specific to this Application/Class of medications

Questionnaire Assessments for Opiate Withdrawal Signs and Symptoms

- Clinical Opiate Withdrawal Scale (COWS):
 - Completed by site personnel at study site
 - 11-item questionnaire
 - Total scores used to assess overall severity of withdrawal
 - (mild= 5 to 12; moderate= 13 to 24; moderately severe= 25 to 36; severe >36)
 - V9231 and V9232 The COWS assessment was to be performed at:
 - Visit 2 (Day 1) (at pre-dose and at 60, 90, 120 minutes post dose [$\pm$ 10 minutes])
 - Visit 3 (Week 1), Visit 4 (Week 2), Visit 5 (Week 4), Visit 6 (Week 8), and Visit 7 (Week 12) (or at Early Termination), at any time during the visit
 - If a COWS total score was $\geq$ 5 or indicated a worsening of withdrawal symptoms, the Investigator or designee was to complete a supplemental Elevated COWS Evaluation Form
 - Data analysis:
 - Summary statistics of the total COWS score (sum of scores on all items) and change from baseline to each scheduled visit were calculated by treatment group.
 - Plots of means of the absolute value (and their standard deviation) over time were presented by treatment group.
 - Analysis of COWS score were performed excluding abdominal pain
- Subjective Opiate Withdrawal Scale (SOWS):
 - Completed by
 - 16-item questionnaire, 5-point rating scale (0=not at all; 1=a little; 2=moderate; 3=quite a bit; and 4=extreme)
 - Used to identify subjects with possible opioid withdrawal
 - Scores do not correlate with specific levels of withdrawal
 - Useful to identify and track potential opioid withdrawal symptoms
 - If a SOWS assessment indicated worsening of withdrawal symptoms, the Investigator or designee completed a supplemental Elevated COWS Evaluation Form to further assess for opioid withdrawal and an unscheduled follow-up COWS assessment was administered as deemed necessary by the Investigator
 - The SOWS assessment was to be performed at:
 - Visit 2 (Day 1) (at pre-dose and at 1 hour post dose [$\pm$ 10 minutes])
 - Between Visit 2 (Day 1) and Visit 4 (Week 2) (ie, first 14 days on study drug) SOWS was to be performed daily by the subject. Subjects performed the SOWS approximately 1 hour after dosing study drug
 - Visit 4 (Week 2), Visit 5 (Week 4), Visit 6 (Week 8), and Visit 7 (Week 12) or Early Termination, and at any time during the visit

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- Means of the total SOWS score were calculated for each week using the formula:
(Total of week's SOWS scores) / (Number of days of observation for the week)
 - Summary statistics of the total SOWS score and change from baseline to each scheduled visit were calculated by treatment group.
 - If multiple records were available in a day, the highest total score was used

Pain Assessments

- 11-point Numeric Rating Scale (NRS): measurement of severity of pain
 - Completed by
 - Rating scale: 0 to 10 (0=no pain and 10=worst possible pain)
 - (0, no pain; 1 to 3, mild pain; 4 to 6, moderate pain; and 7 to 10, severe pain)
 - Studies V9231 and V9232: Completed at the study site at every visit Visit 2 (Day 1) and through Visit 7 (Week 12) or Early Termination
 - Data analyses:
 - Summary statistics of the NRS score for pain evaluation and change from baseline to each scheduled visit were calculated by treatment group.
 - Plots of means (standard deviation) over time by treatment group
 - Summary of outliers (number and percentage) by treatment group
- Opioid Analgesics: assessment of pain based on change in average total daily and weekly dose of opioids from baseline
 - Opioid data used for analyses were:
 - (1) Electronic Data Capture (EDC) data
 - (2) eDiary data
 - (3) eDiary data excluding discrepant subjects (subjects with discrepant EDC and eDiary data)
 - Discrepant data were defined as TDD data in eDiary >200% of EDC data for any ≥ 5 days during the Treatment Period
Note: Review of opioid data to identify those that met criteria for discrepant data was conducted prior to unblinding
 - Data analysis:
 - Change in weekly dose of opioid data by treatment group for the 3 datasets (eDiary data without discrepant subjects was designated as the main analysis)

8.4. Safety Results

Deaths

Nine deaths occurred during the naldemedine clinical trials relevant to the proposed indication—5 in the naldemedine group and 4 in the placebo group (summarized in Table 65). Eight of the 9 deaths (4 in each group) occurred during Study V9235, the 52-week safety trial,

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and 1 death (in the naldemedine group) occurred during the 12-week trials. No deaths occurred in Phase 1 or Phase 2 trials.

All deaths, except Subject 52415-004, who died 97 days after study discontinuation due to fatal TEAE of adenocarcinoma, occurred while subjects were active clinical trial participants.

In 4 cases, the fatal SAE was not considered by the Applicant to be treatment-emergent because the calculated AE onset was >14 days after “last known dose” of study drug. However, these calculations were based on imputed data using flawed methodology. In all 4 cases, medication bottles were not returned to the study site for accountability. Therefore, the Applicant imputed the date of last dose of study drug as the last dose prior to the subject’s last study visit (last accounting of drug doses). However, the Applicant confirmed that all 4 of these subjects were actively participating in the trial at the time of AE onset and received a per-protocol supply of medication at their last study visit. Only 1 of the 4 subjects missed the last study visit prior to AE onset—Subject 52352-002 (cardiopulmonary arrest presumed to be caused by accidental overdose) who missed the last scheduled study visit 7 days prior to AE onset. Assuming regular treatment compliance, all 4 of these fatal AEs were treatment-emergent.

None of the 9 deaths were considered by the Investigator to be related to study treatment. Four events (2 in each treatment arm) were adjudicated by the CAC as cardiovascular deaths.

Six deaths (3 in each treatment arm) were unwitnessed cardiac/cardiopulmonary arrests, of which 3 deaths (1 in the naldemedine arm and 2 in the placebo arm) were adjudicated by the CAC as MACE. No post-mortem evaluation was performed in any of these 6 cases. In general, minimal clinical information was available, and all assigned causes of death for these subjects were presumptive, without any supportive data.

As part of the safety evaluation, data from other naldemedine OIC clinical trials, including phase 3 trials for patients with cancer-related pain and the long-term open-label phase 3 clinical trial (Study 1336V9238) in adults with non-cancer pain (Japan only), were assessed for evidence of previously unrecognized safety signals. In studies of subjects with cancer-related pain, deaths were generally related to subjects’ underlying malignancy, without evidence of treatment effect. In Study 1336V9238 (V9238), one death (unwitnessed event of unknown cause) occurred in a 51-year-old male after 308 days of naldemedine exposure. A more detailed description of this event is included the narratives below.

Table 67: Summary of Deaths in Phase 3, Placebo-Controlled Naldemedine Clinical Trials

Treatment Arm	Subject ID	Age(yrs)/Sex	AE Onset (Day)	On Study Drug	Cause of Death	Reviewer Comment
Naldemedine	22359-018	37/F	9	Yes	"Overdose"-presumed <i>Cardiopulmonary arrest</i>	Unwitnessed death; presumptive diagnosis of overdose without confirmatory data†
	52387-009	58/F	155	UNK*	COPD exacerbation	In-hospital death in patient with pre-existing COPD
	52415-004	52/F	72	Yes	Adenocarcinoma of the lung	Fatal TEAE with study discontinuation due to event (and other non-fatal SAEs); death on day 169
	52375-007	53/F	350	UNK*	"CVA"-presumed <i>Cardiopulmonary arrest</i>	Unwitnessed death; presumptive diagnosis of cerebrovascular accident with no confirmatory data†
	52449-005	49/M	346	UNK*	Myocardial infarction"-presumed <i>Cardiopulmonary arrest</i>	Unwitnessed death (found in bathroom); presumptive diagnosis of overdose without confirmatory data†
Placebo	52352-002	52/M	50	UNK*	"Overdose"-presumed <i>Cardiopulmonary arrest</i>	Unwitnessed death (found in bed); presumptive diagnosis of overdose without confirmatory data†
	52437-005	64/M	28	Yes	"Cardiac arrest" <i>Cardiopulmonary arrest</i>	Unwitnessed death; presumptive diagnosis of cardiac arrest without confirmatory data†
	52442-017	49/F	31	Yes	"Arteriolosclerosis"-presumed <i>Cardiopulmonary arrest</i>	Found dead at home
	52446-013	78/F	175	Yes	Cerebrovascular accident	In-hospital death due to CVA

(Source: Reviewer's table)

Abbreviations used in table: COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; UNK, unknown

* The last day of study drug administration unknown because study medication bottles were not returned to the clinical site for accountability. The Investigator imputed the date of last study drug administration as the last date confirmed by the clinical trial site—the last dose prior to the subject's last visit. These subjects were active clinical trial participants at the time of death. A new supply of study medication would have been dispensed at the subject's last visit. Assuming regular treatment compliance, these events are all treatment-emergent (<14 days after last dose). Subject 52352-002 would likely have been off-treatment due to missed visit 7 days prior to death.

†No investigative clinical data (i.e., laboratory, radiologic, or other diagnostic procedure) and no post-mortem examination

NARRATIVES OF DEATHS

Naldemedine (n=5)

- Subject 22359-018, a 37-year-old female was reported to a sudden death due to unwitnessed cardiopulmonary arrest on Day 9. The subject was found unresponsive after an unwitnessed event. The subject was apneic and pulseless when emergency medical services arrived. Cardiopulmonary resuscitation was initiated, including administration of naloxone. In the emergency department, global hypoxic brain injury was diagnosed by CT scan, and medical care was withdrawn. The cause of death was listed as drug overdose and cardiopulmonary arrest. No diagnostic or clinical information was available to support this diagnosis. The only toxicology studies obtained were an acetaminophen and ethanol level. No other drug levels were obtained. No autopsy was done.

Prior medical history included obesity (BMI = 32.1 kg/m²), osteoarthritis, degenerative disc disease, insomnia, peripheral neuropathy, depression, anxiety, bipolar disorder, attention deficit hyperactivity disorder, hypertension, and headaches. The subject also had a history of suicide attempts, prior history of methadone overdose, and social history notable for current tobacco use and occasional marijuana use.

Reviewer comment: The cause of this unwitnessed event of cardiopulmonary arrest resulting in death is unknown. No toxicology studies or post-mortem evaluation were performed, and the available data do not provide diagnostic information. Therefore, a cardiovascular event cannot be excluded. This case is included in assessments of MACE risk, as well as risk of overdose.

- Subject 52387-009, a 58-year-old female with fatal event of COPD exacerbation (onset Day 155). The subject died during the hospital admission on Study Day 162 (hospital day 8). The cause of death was acute exacerbation of COPD with tobacco use reported as a contributing factor.

Prior medical history included COPD, obesity (BMI=37.3 kg/m²), cardiac catheterization, hypothyroidism, fibromyalgia, intervertebral disc herniation, depression, anxiety, menopause, and restless leg syndrome. No autopsy was done.

Earlier in the study (Day 87), the subject also had a non-serious, TEAE of peripheral edema that was moderate in severity. No action was taken with the study drug due to the AE of peripheral edema. The edema was reported as resolving at the time of last follow-up. The contact between site personnel and the subject was by phone on Day 126, at which time the subject reported no changes in health or medication.

The last dose of study drug was reported as Day 99 (imputed date based on the subject's last study visit). The subject was actively participating in the clinical trial at the time of SAE onset. No information was provided regarding study treatment during the subject's hospitalization.

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Reviewer comment: This death was caused by an exacerbation of a pre-existing condition. It cannot be determined whether study treatment was a contributing factor in the severity or outcome of this event.

- Subject 52415-004, a 52-year-old, White female with fatal SAE of Stage IV adenocarcinoma of the lung (onset Day 72). The subject presented to the emergency room on Study Day 72 with chest pain and dyspnea and was subsequently hospitalized. Of note, the patient had also presented with dyspnea on Study Day 63, at which time only showed cardiomegaly (no pneumonia). Repeat chest x-ray on Day 72 showed prominent vasculature. The subject was hospitalized from Day 72 to day 78, during which time the subject was diagnosed with multiple SAEs, including the fatal SAE of Stage IV adenocarcinoma.
 - Deep venous thrombosis (popliteal vein) was diagnosed by Doppler ultrasound and confirmed by venogram
 - Pulmonary embolism- venocaval filter placed based on venacavogram
 - Myocardial infarction with abnormal ECG and findings of arterial blockage and ischemia on cardiac catheterization
 - Adenocarcinoma (fatal SAE) was diagnosed initially based on a bloody pericardial fluid sample obtained on Day 76 which demonstrated malignant cells, consistent with adenocarcinoma. Based on additional evaluation determined to be metastatic adenocarcinoma with primary pulmonary malignancy.

Prior medical history included obesity (BMI=35.8 kg/m²), anxiety, B12 deficiency, cervicgia/chronic neck pain, chronic bronchitis (COPD), intervertebral disc herniation and degeneration, depression, bilateral deep vein thrombosis of the lower extremities, edema, fibromyalgia, hysterectomy, migraine headache, muscle spasms, neuropathic pain, osteoarthritis, and pneumothorax syndrome.

Study drug was discontinued during hospitalization on Day 72 (admission to the hospital). The investigator considered the events of pulmonary embolism and myocardial infarction as severe in severity and possibly related to study drug. The investigator considered the event of DVT as moderate in severity and possibly related to study drug. The investigator considered the event of Stage 4 adenocarcinoma as severe in severity and not related to study drug.

Reviewer comment: This subject had multiple diagnoses made during the hospitalization for the fatal SAE. While this reviewer agrees that the fatal SAE of adenocarcinoma is unrelated to study treatment. The other SAEs of deep venous thrombosis, pulmonary embolism, and myocardial infarction represent events of interest and are discussed elsewhere.

- Subject 52375-007, a 53-year-old female, was found dead at home on Study Day 350. An autopsy was not performed. The cause of the death as captured in the death certificate was suspected cerebrovascular accident. The event was adjudicated by the CAC as an

undetermined cause of death.

Prior medical history included chronic headaches (hemicranias continua), abnormal gait with frequent falls, orthostatic hypotension, restless leg syndrome, bronchitis, sinus infection, septal perforation, knee pain, depression, anxiety, asthma, and postmenopause.

The subject was actively participating in the clinical trial at the time of death.

Reviewer comment: The case is one of the unwitnessed fatal events for which the cause of cardiopulmonary arrest is unknown. No toxicology studies or post-mortem evaluation were performed, and the available data do not provide diagnostic information.

- Subject 52449-005, a 49-year-old male, was found dead in the bathroom on Day 350, presumed to have died 4 days earlier (Day 346). An autopsy was not performed. The cause of death was captured in the death certificate as myocardial infarction due to or as a consequence of diabetes. This event was adjudicated by the CAC as a cardiovascular death.

Medical history included diabetes mellitus type 1, acute myocardial infarction, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, spinal osteoarthritis, cervical radiculitis, cervical spondylosis, chronic back pain, chronic neck pain, rotator cuff syndrome, headaches, anxiety, depression, and overweight (BMI = 27.7 kg/m²).

The subject was actively participating in the clinical trial at the time of death.

Reviewer comment: The case is one of the unwitnessed fatal events for which the cause of cardiopulmonary arrest is unknown. No diagnostic studies or post-mortem evaluation were performed, and the available data do not provide diagnostic information.

Placebo (n=4)

- Subject 52352-002, a 52-year-old male, with death due to cardiopulmonary arrest. The subject was found dead by in his bed. Cause of death was listed as accidental opioid overdose. No laboratory evaluation was performed. No autopsy was done.

The subject had a previous medical history of BMI in the overweight range (BMI=28.1 kg/m²), hypercholesterolemia, type 2 diabetes, lower back pain/ injuries, and peripheral neuropathy.

The subject missed Visit 5 (scheduled on Day 43). The site attempted unsuccessfully to contact the subject on the day of the missed visit and was later informed of the subject's death by the subject's son. The cause of death of "overdose" was presumptive based on the subject's history of chronic opioid use.

Reviewer comment: The case is one of the unwitnessed fatal events for which the cause of cardiopulmonary arrest is unknown. No toxicology studies or post-mortem evaluation were performed, and the available data do not provide diagnostic information. A cardiovascular event cannot be excluded.

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- Subject 52437-005, a 64-year-old male found on Day 28. The subject was found on the bathroom floor by his wife. Upon arrival of EMS, the subject was pulseless and apneic. Cardiopulmonary resuscitation was initiated, including intubation, chest compressions, and administration of naloxone and epinephrine. The electrocardiogram reportedly showed asystole throughout the process, except for a brief period of pulseless electrical activity. Based on advanced directives specifying that the subject did not want intubation, excessive resuscitation, or transportation to a facility, EMS obtained permission to cease resuscitative events. The presumed etiology was cardiac. The cause of death was listed as cardiac arrest and atherosclerotic cardiovascular disease. The event was adjudicated by the CAC as a cardiovascular death.

Prior medical history was notable for atrial fibrillation, COPD, degenerative intervertebral disc disease, depression, hypercholesterolemia, hypertension, osteoarthritis, lower extremity edema, heavy tobacco use (40 cigarettes per day since 1960), and BMI in the overweight range (BMI=28.8 kg/m²).

Reviewer comment: The case is one of the unwitnessed fatal events for which the cause of cardiopulmonary arrest is unknown. No diagnostic studies or post-mortem evaluation were performed, and the available data do not provide diagnostic information.

- Subject 52442-017, a 49-year-old White female with an SAE found dead at home by her husband on Day 28. Emergency services were contacted but the subject was assessed to be deceased and no resuscitation was performed. No autopsy or examination was done. The cause of death was listed as complication of atherosclerotic heart disease (Applicant AE term “arteriosclerosis”). The event was adjudicated by the CAC as a cardiovascular death.

Prior medical history included obesity (BMI=37.1 kg/m²), diabetes mellitus type 2 with diabetic neuropathy, COPD, asthma, anxiety, anemia, GERD, lumbar intervertebral disc degeneration, and hemorrhoids.

Reviewer comment: The case is one of the unwitnessed fatal events for which the cause of cardiopulmonary arrest is unknown. No diagnostic studies or post-mortem evaluation were performed, and the available data do not provide diagnostic information.

- Subject 52446-013, a 78-year-old female, experienced a fatal cerebrovascular accident (CVA) on Study Day 175. The subject was found unresponsive in the bathroom by her husband. Head CT showed likely basilar thrombosis. The initial treating hospital administered aspirin and ceftriaxone sodium. Based on the NIH stroke scoring system, TPA was not given. The subject was transferred another facility where a CT perfusion was performed, demonstrating abnormality in the cerebral blood flow in the brain stem. CT angiogram showed occlusion of the basilar artery with intraluminal thrombus in the distal basilar artery and perfusion abnormalities involving the midbrain and infero-posteromedial thalami bilaterally. Several attempts were made to perform a mechanical thrombectomy procedure, but were unsuccessful due to inability to catheterize either vertebral artery or

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the right subclavian artery. The family requested initiation of comfort care, and the subject expired on Day 179. The event was adjudicated by the CAC as a cardiovascular death.

Medical history included obesity (BMI=38.1 kg/m²), hypercholesterolemia, hypertension, asthma, osteoarthritis, bilateral knee replacements, multiple fractures, peripheral neuropathy, GERD, hiatal hernia (post repair), and tremor.

The subject was actively participating in the clinical trial at the time of AE onset. The drug was withdrawn following hospitalization.

Reviewer comment: This is a confirmed case of MACE in a subject receiving placebo.

Additional Narrative: Study V9238 (open-label study in Japanese subjects only)

- Subject ID: 2NW002- 51-year-old male (50 years old at study enrollment) with with unwitnessed death of unknown cause on Study Day 309. Prior medical history was most notable for pulmonary embolism (PE) and deep vein thrombosis (DVT), for which the subject was on anticoagulation. Other medical history included spinal osteoarthritis, muscle spasms, insomnia, and tinnitus. BMI was 25.2 kg/m² (overweight). Concomitant medications included warfarin (see below), celecoxib, eperisone (muscle antispasmodic), etizolam, somazolam, sennoside laxative, neurotrophin, diclofenac topical gel, ramelteon, amlodipine, mepivacaine injection, magnesium oxide, and acetaminophen. Opioid medications included morphine, tramadol, and transdermal fentanyl.

At the time of enrollment, the subject was on warfarin treatment for prophylaxis of thrombosis due to prior history of PE and DVT. Prior to the event, in Month 7 of study treatment, warfarin treatment was interrupted for 1 week due to prolonged prothrombin time (PT), then 3 weeks later, the subject's anticoagulant medication was switched from warfarin to edoxaban tosilate hydrate. Two months later (Study Day 308), the subject was found dead at home. An autopsy could not reveal the cause of death.

During study participation, the subject also experienced non-serious AEs of diarrhea (onset Day 2), vomiting (onset Day 114), contusion (onset Day 223), and muscle spasms (onset Day 225).

Reviewer Comment: Study V9238 is an open-label, single-arm study. Therefore, there is no comparator to detect increased risk of treatment over background event rate. This fatal event represents a case of MACE and another sudden, unwitnessed cardiac/ cardiopulmonary arrest of unknown cause. This subject did not have reported history of significant cardiac risk factors, although concomitant medications include amlodipine, which suggests possible history of hypertension. The autopsy was uninformative and did not reveal evidence of recurrence of PE or other thrombotic event.

8.4.2. Serious Adverse Events

A total of 174 subjects in Phase 3 placebo-controlled safety population had ≥ 1 treatment-emergent serious adverse event (SAE)—83 in the naldemedine arm (7.1%) vs. 91 in the placebo arm (7.8%). A total of 143 SAEs were reported, of which 18 were identified by this reviewer as definitely having an AE onset > 5 days after discontinuation of treatment (i.e., not “on-treatment”). (Table 68)

Not surprisingly, the total number of SAEs and percentage of subjects with ≥ 1 SAE were 3 to 4-fold higher in Study V9235 than Studies V9231 and V9232.

All on-treatment SAEs (i.e., during the period from the first dose of study drug to 5 days after drug discontinuation) are shown in Table 67 and Table 68 [SAEs that occurred in ≥ 1 subjects are summarized in Table 67, and SAEs occurring in only a single individual are listed in Table 68.] In both groups, the most common SAEs were pneumonia and arthritis (the majority of arthritis SAEs were classified as serious because subjects were hospitalized for surgical procedures).

Table 68: Incidence of SAEs and Numbers of Events in Placebo-controlled Phase 3 Clinical Trials

		Naldemedine		Placebo	
		n (%)	# of events	n (%)	# of events
Treatment-emergent	All Phase 3 Controlled Studies	83 (7.1)	119	91 (7.8)	124
	Studies V9231 & V9232	23 (4.2)	31	18 (3.3)	22
	Study V9235	60 (9.7)	88	73 (11.8)	102
On-treatment*	All Phase 3 Controlled Studies	82 (7.1)	114	90 (7.7)	116
	Studies V9231 & V9232	19 (3.5)	25	16 (2.9)	19
	Study V9235	63 (10.1)	89	74 (12.0)	97

*On-treatment is defined as events occurring between administration of the first dose of study drug to < 5 days after study drug discontinuation.

Table 69: On-Treatment SAEs occurring in > 1 Subject in Placebo-controlled Phase 3 Clinical Trials

(*Note: Because most of events were infrequent, percentages are only provided for SAEs occurring in $\geq 0.5\%$ of at least 1 of the treatment arms for either study type-shaded in table.)

Serious Adverse Event (SAE)	Studies V9231&V9232 (12-Week Studies)		Study V9235 (52-Week Study)		Pooled Phase 3 Safety Population	
	Naldemedine (N=542)	Placebo (N=546)	Naldemedine (N=621)	Placebo (N=619)	Naldemedine (N=1163)	Placebo (N=1165)
Pneumonia	0	3 (0.5)	8 (1.3)	6 (1.0)	8 (0.5)	9 (0.8)
Arthritis	0	1 (0.2)	6 (1.0)	6 (0.8)	6 (0.5)	6 (0.5)
COPD	2 (0.4)	1 (0.2)	3 (0.5)	4 (0.6)	5 (0.4)	5 (0.4)
Back pain	1 (0.2)	0	2 (0.4)	5 (0.8)	3 (0.3)	5 (0.4)
Overdose (opioid*)	1 (0.2)	1 (0.2)	3 (0.5)	0	4 (0.3)	1 (0.1)
Myocardial infarction	0	0	4 (0.6)	1 (0.2)	4 (0.3)	1 (0.1)
Abdominal pain	1	0	2	2	3	2
Angina	0	1	0	3	0	4

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Serious Adverse Event (SAE)	Studies V9231&V9232 (12-Week Studies)		Study V9235 (52-Week Study)		Pooled Phase 3 Safety Population	
	Naldemedine (N=542)	Placebo (N=546)	Naldemedine (N=621)	Placebo (N=619)	Naldemedine (N=1163)	Placebo (N=1165)
Cellulitis	0	0	2	3	2	3
Chest pain, NOS	0	0	1	3	1	3
Congestive heart failure	1	0	1	2	2	2
Sepsis	0	1	1	2	1	3
Bone fracture	0	0	1	2	1	2
Cerebrovascular accident	0	0	2	1	2	1
Chest pain, musculoskeletal	0	1	1	1	1	2
Cholelithiasis/ Bile duct stone	1	0	2	0	3	0
Dehydration	2	0	0	1	2	1
Mental status changes	0	1	1	1	1	2
Non-small cell lung cancer	0	0	2	1	2	1
Peripheral vascular disease	0	0	2	1	2	1
Postoperative/ Incision site infection	0	0	0	3	0	3
Psychosis	0	1	1	1	1	2
Renal impairment/failure	1	0	0	2	1	2
Respiratory failure	0	0	1	2	1	2
Spinal stenosis	0	0	3	0	3	0
Syncope/ Loss of consciousness	0	2	1	0	1	2
Toxic/metabolic encephalopathy	0	0	2	1	2	1
Urinary tract infection/Urosepsis	1**	0	0	2	1	2
Vomiting	0	1	1	1	1	2
Appendicitis	1	0	1	0	2	0
Asthma/bronchospasm	0	0	1	1	1	1
Bladder cancer	0	1	0	1	0	2
Deep vein thrombosis	0	0	1	1	1	1
Gastritis	1	0	0	1	1	1
Intervertebral disc disease	0	0	0	2	0	2
Neck pain	0	0	2	0	2	0
Pulmonary embolism	0	0	2	0	2	0
Spondylolisthesis	0	0	1	1	1	1
Tooth infection/abscess	0	0	0	2	0	2

(Source: Reviewer's table)

* At least 1 opioid medication was identified as a causative agent, but the event was not necessarily limited to overdose of only opioid medications (Table 72)

** The SAE of urinary tract infection in the naldemedine was not a TEAE. Urinary tract infection was present at baseline (pre-treatment) but onset was reported as Study Day 7 (day of hospitalization).

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Table 70: On-treatment SAEs Reported in a Single Patient in the Pooled Phase 3 Placebo-Controlled Safety Population

Clinical Trial	SAE Terms by Treatment Arm	
	NALDEMEDINE	PLACEBO
Studies V9231 & V9232	Acute enterocolitis Duodenitis/Enteritis Herpes zoster Hypersensitivity Hypomagnesemia (with dehydration) Lymphadenopathy Patent ductus arteriosus Sciatica Supraventricular tachycardia Ventricular extrasystoles Weakness of lower extremities Wrist sprain	Device failure Hypotension Seizure/convulsion Sick sinus syndrome
Study V9235	Adenocarcinoma colon Arthralgia Bacterial arthritis Breast cancer Bronchitis Carotid artery stenosis Cervicobrachial syndrome Constipation Device dislocation Dyspnea Femoral artery occlusion Gastric volvulus Headache Hepatitis Hyperkalemia Muscle spasms/twitching Myalgia Necrotic/infected skin ulcer Orthostatic hypotension Otitis Panic attack Parotitis (with sepsis) Pneumothorax (with lung carcinoma) Sickle cell anemia with crisis Stress Subcutaneous abscess Tachycardia, NOS Tenosynovitis (dog bite)	Arteriolosclerosis (death) AV block, first degree Bladder prolapse Cardiac arrest (death) Carpal tunnel syndrome Cholecystitis Colitis Depression Dyspepsia/GERD Flatulence Gastric varices Impaired gastric emptying Localized infection, NOS Mitral valve incompetence Necrotizing fasciitis Nephrolithiasis Overdose (non-opioid only) Pleurisy Rhabdomyolysis Road traffic accident/whiplash injury Sinus polyp Small cell lung cancer Small intestinal obstruction Spinal claudication Suicidal ideation Surgical failure (of remote hip replacement) Traumatic hematoma Transient ischemic attack Urinary retention Viral infection

(Source: Reviewer's table)

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Gastrointestinal SAEs were reported in 23 subjects with in the pooled phase 3 placebo-controlled population, with similar numbers of events in both treatment arms (12 in the naldemedine group and 11 in the placebo arm). Narratives for these events are provided in Table 53.

In general, the types of GI SAEs reported were representative of the overall GI-related TEAE data (see Sections 8.4.4 and 8.4.5), in which early naldemedine-GI toxicity was noted, and other types of GI events were also commonly due to subject's opioid medications and other underlying conditions. Notably, the majority of patients in both groups with GI-related SAEs were female (10/12 in the naldemedine arm and 10/11 in the placebo arm).

Pain-related SAEs comprised the largest group of SAEs in Study V9235; however, only 4 on-treatment pain-related SAEs were identified that occurred during Studies V9231 and V9232—2 in the naldemedine arm (Subject 12205-002 with worsening back pain and Subject 22326-007 with sciatica) and 2 in the placebo arm (Subject 12211-003 with osteoarthritis aggravation and Subject 22302-003 with musculoskeletal chest pain).

By contrast, pain-related SAEs were reported in 36 subjects in Study V9235 (2.9%)— 17 subjects in the naldemedine group and 19 subjects in the placebo group. For 20 of these subjects (10 in each group), these events represented worsening of their underlying joint disease, resulting in surgery. In the naldemedine group, 7 of the 10 surgeries were performed after Study Day 120 (the other 3 were performed on days 37, 49, and 63), while the earliest surgery in the placebo group was performed on Day 120. The higher incidence of pain-related SAEs in the 52-week, compared to the 12-week studies, would be expected due to progression of subjects' underlying condition over time. Review of these data did not identify any unexpected differences between treatment arms, with the exception of appendicitis, which was reported only in 2 naldemedine-treated subjects (1 in the 12-week studies and 1 in the 52-week study). The number of SAEs of appendicitis is too low and the background rate of appendicitis is too high for this to be considered a safety concern that requires any specific assessments and can be addressed by routine post-marketing surveillance.

There were no organ-systems for which SAEs occurred at a higher frequency in the naldemedine group, with the exception of hepatobiliary disorders (4 in the naldemedine group vs. 1 in the placebo group), and these events did not appear to be treatment-related.

Of the other non-GI-related SAE preferred terms, this reviewer identified 3 notable types of SAEs that occurred more frequently in the naldemedine group, though the overall rate of all of these events were low (<0.5%):

- Myocardial infarction (4 in the naldemedine arm vs. 1 in the placebo arm)
- Pulmonary embolism (2 in the naldemedine group vs. 0 in the placebo arm)
- Overdoses (4 subjects in the naldemedine group vs. 2 in the placebo arm)

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Myocardial infarction and pulmonary embolism were considered notable due to their relevance to MACE assessments. Although a treatment difference was observed based on AE preferred terms, the number of myocardial infarctions based on CAC adjudication was the same in both groups (3 events per arm), though one of the 4 events in the naldemedine arm with the assigned the preferred AE term “myocardial infarction” was not adjudicated by the CAC. Another of these myocardial infarction SAEs was fatal (Subject 52449-005 in the naldemedine arm), and this event was classified by the CAC as “cardiovascular death.” In the placebo arm, one event of “angina unstable” was classified as a myocardial infarction by CAC adjudication, and 2 SAEs were classified as cardiovascular death (Subject 52442-017 with “arteriosclerosis” and 52437-005 with “cardiac arrest”). Also, one SAE in each arm was classified as a myocardial infarction, type 2, by the CAC (i.e., myocardial ischemia secondary to another event—Subject 12322-008 with “supraventricular tachycardia” and 22341-011 with “syncope and hypotension.” These events are discussed in more detail in Section 8.5.1.

Overdoses represent an event of interest due as a potential risk if opioid dosages are acutely increased due to decreased opioid efficacy by naldemedine. As noted above, 6 subjects with on-treatment SAEs of overdose involving opioid medication(s) were reported (4 in the naldemedine arm and 2 in the placebo arm). In addition, this reviewer identified 6 additional cases (3 in each group) that are consistent with either definite or possible opioid overdose through a search of narratives coded under related AE terms (e.g., toxic encephalopathy, metabolic encephalopathy, mental status change, altered level of consciousness, and respiratory depression) and for subjects treated with naloxone. During the review of these cases, a high degree of overall morbidity, concomitant mental illnesses, and polypharmacy was observed across subjects in both arms, and no treatment difference could be identified. Narratives for these 12 subjects (7 naldemedine, 5 placebo) are provided in Table 72.

This reviewer also identified the following 16 SAEs of interest, based upon overall TEAE data, possible mechanism, or previously identified safety concerns either for this drug or the PAMORA drug class. Narratives and reviewer comments for these events are provided in Table 71.

- Subject 10602-002: Allergic reaction/hypersensitivity (possible anaphylaxis; discussion in Section 8.4.4)
- Subject 12302-011: Premature ventricular contractions in triplets
- Subject 12322-008: Supraventricular tachycardia
- Subject 12333-005: COPD exacerbation
- Subject 50409-006: Congestive heart failure (2 events)
- Subject 50709-005: Sinus tachycardia
- Subject 52325-016: Hepatitis (discussed in section 9.4.7, Liver Events)
- Subject 52331-005: Stress
- Subject 52334-017: Peripheral arterial occlusive disease, skin necrosis
- Subject 52349-008: Femoral artery occlusion

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- Subject 52362-021: Sickle cell anemia with crisis
- Subject 52415-004: Pulmonary embolism, deep venous, thromobosis, myocardial infarction, adenocarcinoma
- Subject 52428-007: Pulmonary embolism, pneumonia

One subject (12305-005) with patent ductus arteriosus underwent cardiac catheterization for PDA closure on Study Day 21. Although this procedure was not planned at the time of screening, medical records from the treating cardiologist specifically indicate that the subject experienced no worsening in this pre-existing condition after initiation of study treatment.

Table 71: Gastrointestinal-Related SAEs in all Phase 3 Placebo-Controlled Clinical Trials

Treatment Arm	Subject ID	Verbatim AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
Naldemedine (n=12)	10103-001	Abdominal Pain	65/M	28	5	Mild/	Completed	Resolved
		• Hospitalization for “strong abdominal pain” associated with diarrhea • Prior history of diverticulosis, hiatal hernia, and peptic ulcer disease • No specific diagnosis/etiology reported or evident from diagnostic testing • Only treatment specified was morphine <i>Reviewer comment: Possible naldemedine AR; however, AE onset at Week 4 of treatment, short AE duration, and self-resolution of symptoms despite ongoing treatment suggest alternate etiology, possibly due to a pre-existing condition</i>						
	12209-005	Appendicitis	31/F	72	7	Moderate	Interrupted/ Completed	Resolved
		• Admitted to the hospital for abdominal pain, cramping, and vomiting, diagnosed with appendicitis based on CT finding of fat stranding around the appendix. • Laparoscopic appendectomy was performed on Day 78 • Study treatment was interrupted during hospitalization due to the event <i>Reviewer comment: Agreement with Investigator assessment that this SAE of appendicitis was unlikely related to study treatment.</i>						
	12333-015	Dehydration	55/F	24	2	Severe	Withdrawn	Resolved
		• Minimal information for this SAE was available except that the subject was admitted for dehydration associated with nausea • There is no information regarding precipitating events, full scope of symptoms, evaluation performed, or treatment provided • The subject withdrew from the study on Day 31 because she “no longer wanted to participate”; the date of the last dose of study treatment is not clear <i>Reviewer comment: This event is presumed to be GI-related based on the reported association with nausea symptoms. However, insufficient information is available to assess the nature of the event or the relationship to study treatment, including whether this represents a significant sequela of GI toxicity (i.e., dehydration secondary to diarrhea, etc.). Of note, this is the only AE reported for the subject.</i>						

Treatment Arm	Subject ID	Verbatim AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
	22357-003	Acute Enterocolitis	56/F	1	3	Severe	Withdrawn	Resolved
- Hospitalized with vomiting, upper abdominal pain, and diarrhea (diagnosed as enterocolitis), with sudden onset within 2 hours of the first dose of study drug - Treatment included intravenous hydration, morphine, and lorazepam - Abdominal CT consistent with non-specific enterocolitis <i>Reviewer comment: Agree with the Investigator that this event was definitely related to study treatment with typical presentation of a naldemedine GI AR.</i>								
	22359-015	Gastritis, Duodenitis, Cholelithiasis	66/F	38	5	Mild/Moderate	Completed	Resolving
- Hospitalized for abdominal pain and vomiting on Day 38 - Prior medical history was notable for obesity (BMI = 37.4 kg/m²), hyperlipidemia, and menopause - Radiologic findings included partially calcified structure on the right side of the abdomen and moderate amount of stool in the colon on abdominal X-ray, and large gallstone and fatty liver on abdominal CT; hepatobiliary iminodiacetic acid scan was negative. - Gastritis and duodenitis were noted on esophagogastroduodenoscopy - Treatment included intravenous pantoprazole. <i>Reviewer comment: Although this GI event could be related to naldemedine treatment, an AR is less likely given the relatively late onset, short AE duration, and self-resolution of symptoms. GI diagnoses of gastritis and/or cholelithiasis would not be unexpected in this subject with multiple risk factors for these conditions.</i>								
	50411-004	Cholelithiasis	51/F	147	23	Severe	Interrupted/Completed	Resolved
- The subject experienced 2 episodes of cholelithiasis during study participation—on Day 104 (non-SAE) and day 147 (SAE). - The first event (onset Day 104) presented with obstructive jaundice (nausea, elevated bilirubin) and the subject underwent gallstone removal via an endoscopic retrograde cholangiopancreatography. - On Day 147, the subject presented with acute onset of right upper quadrant abdominal pain and nausea, as well as elevated alkaline phosphatase and GGT, and an inpatient procedure for gallstone removal was performed - Study treatment remained unchanged during the SAE but was interrupted during the first event of cholelithiasis. Note that this subject completed the study and was erroneously reported in the narrative to have withdrawn from the study. <i>Reviewer comment: This is one of 3 SAEs in the naldemedine group for cholelithiasis/bile duct stone, and 1 of 2 subjects with recurrent episodes during study participation. In the placebo group, there was 1 SAE for cholecystitis. However, for all TEAEs, there were 4 subjects in each group with</i>								

Treatment Arm	Subject ID	Verbatim AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
		<i>cholelithiasis/cholecystitis, and all subjects had clear risk factors. A causal relationship with study treatment does not seem likely.</i>						
	52216-005	Abdominal Pain	50/F	1	7	Moderate	Withdrawn	Resolved
		- The subject experienced sudden onset of epigastric pain, associated with nausea and vomiting few hours after the first dose study drug (Day 1) and was hospitalized from Study Day 2 to 7 with resolution of symptoms. The subject was on an established laxative regimen at baseline. - Notable findings on evaluation include BP 147/93, pulse 95, and ALT 204 U/L; Abdominal CT showed possible wall thickening of sigmoid colon. - Treatment included metronidazole for presumed colitis, as well as duloxetine, cyclizine, acetylsalicylic acid, pregabalin, morphine, and prucalopride. - The study drug was discontinued on Day 1 and subject was withdrawn from the study on the same day due to this SAE <i>Reviewer comment:</i> <i>This event is consistent with a treatment-related GI reaction and is supported by the rapid onset of symptoms following administration of the first dose. In addition, the patient's symptoms (abdominal pain, nausea, and vomiting) are typical of naldemedine GI toxicity, which has not been associated with demonstrable tissue injury and resolve without sequelae following treatment discontinuation, as observed with this subject. The changes in the sigmoid colon seen on CT can be attributed to chronic constipation, and a diagnosis of colitis is less likely.</i> <i>Of note, the elevated ALT level reported with the SAE was not included among study data, and this subject was not flagged as a patient with transaminase elevation. No follow-up data are available. Therefore, a treatment-related transaminitis cannot be ruled out.</i>						
	52225-006	Cholelithiasis/ Bile Duct Stone	46/F	85 242	148 44	Severe	Interrupted/ Completed	Resolved
		- The subject was diagnosed with gallstones on Study Day 85 and underwent laparoscopic cholecystectomy on Study Day 232, and 10 days later (Day 242), she was hospitalized due to acute onset of severe abdominal pain due to a bile duct stone - Prior medical history includes obesity (BMI=37.3 kg/m²) - Evaluation was notable for elevated bilirubin 29 umol/L (0-21), alanine aminotransferase 289 u/L (0-40 u/L), alkaline phosphatase 178 u/L (35-104 u/L) - Treatment included hyoscine butylbromide, morphine, mucogel, omeprazole, paracetamol, and tramadol; and by Day 242, the stone was assumed to have passed spontaneously - Study treatment was interrupted multiple times during study participation due to both serious and non-serious AEs, including during the SAE of bile duct stone <i>Reviewer comment:</i> <i>This is one of 3 SAEs in the naldemedine group for cholelithiasis/bile duct stone, and 1 of 2 subjects with recurrent episodes during</i>						

Treatment Arm	Subject ID	Verbatim AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
		<i>study participation. In the placebo group, there was 1 SAE for cholecystitis. However, for all TEAEs, there were 4 subjects in each group with cholelithiasis/cholecystitis, and all subjects had clear risk factors. A causal relationship with study treatment does not seem likely.</i>						
	52334-008	Constipation	64/F	298	361	Severe	Completed	Resolved
		- Following surgery for a left total knee replacement (Day 293), the subject received multiple opioid medications, including hydromorphone, oxycodone, morphine, and oxycodone/ paracetamol, and developed severe constipation (no BM for 12 days), for which the subject was hospitalized from Day 298 to 305. - Treatment included polyethylene glycol electrolyte solution and enemas. <i>Reviewer comment: This SAE of constipation occurred in a naldemedine-treated subject. Although this severe exacerbation of OIC can be attributed to increased opioid medications after surgery, it should be noted that the subject's naldemedine treatment remained uninterrupted during the perioperative and post-surgical periods.</i>						
	52348-009	Gastric Volvulus	63/F	234	41	Severe	Completed	Resolved
		- Hospitalizations on Day 234 and Day 274 for gastric outlet obstruction secondary to gastric volvulus due to displacement of prior gastric fundoplication - Abdominal CT showed gastric outlet obstruction secondary gastric volvulus and retroflexion views of the proximal stomach suggested supradiaphragmatic positioning of the fundoplication - An esophagogastroduodenoscopy was performed with gastric suctioning and nasogastric (NG) tube placement. Other treatment included intravenous hydration, ondansetron, and pain management with hydromorphone and ketorolac. - Repeat imaging showed that the gastric volvulus persisted without gastric outlet obstruction, after which the subject refused percutaneous endoscopic gastrostomy tube placement against medical advice and was discharged on Day 236 able to maintain oral intake - Recurrence of the gastric volvulus occurred 38 days later, at which time the subject underwent fundoplication repair <i>Reviewer comment: Use of PAMORAs is contraindicated in patients with known or suspected gastrointestinal obstruction and at increased risk of recurrent obstruction [7,8]. Although a causal relationship between naldemedine treatment and the underlying etiology of this SAE cannot be established, naldemedine treatment in this subject may have been inappropriate and contributed to the subject's morbidity.</i>						
	52375-003	Abdominal pain	57/F	1	1	Moderate	Withdrawn	Resolved
		The subject experienced acute onset of abdominal pain, nausea, sweating, yawning, increased bowel movements, and restlessness 1 hour after						

Treatment Arm	Subject ID	Verbatim AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
		administration of the first dose of study treatment. • Symptoms worsened despite promethazine treatment, and the subject was sent to the emergency room for management of worsening of abdominal pain and drug withdrawal syndrome. • Treatment included intravenous hydromorphone, ondansetron, and a second dosage of promethazine with improvement in symptoms within a few hours • Baseline COWS score was 0 and increased to 8 and 7 at 90 and 120 minutes post dose, respectively, consistent with opioid withdrawal. • The subject was withdrawn from the study due to the event. <i>Reviewer comment: This SAE represents treatment-related opioid withdrawal with gastrointestinal symptoms. Although the only SAE reported for this subject was the abdominal pain, the treatment in the emergency department was for the syndrome of opioid withdrawal, not just abdominal pain. A non-serious AE of opioid withdrawal was also reported for this subject and is included among the data discussed in Section 8.5.1.</i>						
	52429-001	Vomiting	66/M	125	2	Severe	Completed	Resolved
		• Hospitalization from Day 125 to 127 for gastrointestinal complaints of nausea, vomiting, and diarrhea (onset Day 124) • Prior medical history included morbid obesity (BMI=45.6 kg/m²) obesity, chronic kidney disease, COPD, diabetes, diverticulitis, GERD, gout, mitral valve disorder, cardiomegaly, cardiovascular disease, and pacemaker placement. • On the day prior to admission, the subject was evaluated in the emergency department and received intravenous hydration and treatment with promethazine • Laboratory studies from the emergency department (Day 124) were notable for elevated serum creatinine (1.8 mg/dL) • Inpatient evaluation was notable for leukocytosis. Findings on cardiac assessments and GI imaging were consistent with pre-existing medical conditions and prior events and did not identify a new diagnosis. • Treatment included 1 dose of levofloxacin, intravenous fluids, and ondansetron • Prior to discharge, the subject's creatinine had decreased to 0.9 mg/dL and WBC count had normalized. <i>Reviewer comment: This subject's symptoms of this GI-related SAE are similar to those observed with naldemedine-related reactions; however, the short duration of symptoms despite ongoing treatment suggests that this SAE was not a treatment-related reaction.</i>						
Placebo (n=11)	22306-012	Vomiting	52/F	8	1	Mild	Completed	Resolved
		• The subject was evaluated in the emergency room for vomiting attributed to exacerbation of diabetes (serum glucose 489 mg/dL) • Prior medical history included GERD, obesity, chronic pancreatitis, and Type 2 diabetes mellitus. <i>Reviewer comment: This SAE is a GI event secondary to acute hyperglycemia in a subject with known history of brittle diabetes mellitus. This event occurred in the placebo arm and is provided for comparison to study treatment.</i>						

Treatment Arm	Subject ID	Verbatim AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
	51209-001	GERD	75/F	29	3	Severe	Completed	Resolved
		• Subject was admitted for chest pain diagnosed as GERD • Prior medical history included morbid obesity (BMI=42.6 kg/m²), diabetes mellitus, GERD, duodenal ulcer, asthma, pacemaker implantation, paroxysmal atrial fibrillation • ECG, echocardiography, and laboratory results excluded a cardiovascular event. • Treatment with pantoprazole was started <i>Reviewer comment: This GI-related SAE in a placebo patient was considered by the investigator as possibly related to study drug. Consistent with overall TEAE data, the patient's symptoms of GERD were likely related to opioid-induced GI effects and/or secondary to other underlying conditions such as diabetes mellitus (i.e., diabetic gastroparesis), obesity, etc.</i>						
	52314-011	Impaired Gastric Emptying	64/F	341	15	Severe	Completed	Resolved
		• Hospitalization for gastroparesis secondary to diabetes mellitus type 2 from Day 347 to Day 350, with symptoms of nausea and vomiting for 7 days prior to admission. • Prior medical history included obesity (BMI=34.4 kg/m²), diabetes, chronic renal insufficiency, rheumatoid arthritis, and GERD. • No information regarding evaluation or treatment was provided <i>Reviewer comment: This GI-related SAE in a placebo patient was attributed to the subject's pre-existing condition of diabetes mellitus (i.e., diabetic gastroparesis), and may have been exacerbated by opioid-induced GI effects.</i>						
	52319-017	Gastric varices	63/F	304	30	Severe	Interrupted/ Completed	Resolved
		• Hospitalization for upper gastrointestinal bleeding due to gastric varices • The subject presented with hematemesis and syncopal episode • Medical history included coronary artery disease, prior coronary artery bypass, diabetes mellitus type 1, hypothyroidism, hypertension, pacemaker placement, chronic kidney disease (stage 3) • The subject underwent exploratory laparotomy and was discharged on Day 313, and was readmitted on Day 328 for splenectomy and diaphragmatic repair for treatment of symptomatic gastric varices • Study treatment was interrupted for 2 days during her initial hospitalization <i>Reviewer comment: This GI-related SAE in a placebo patient is included for comparison with study treatment and demonstrates the high degree of overall morbidity in this study population.</i>						
	52333-015	Small intestinal obstruction	54/F	16	3	Severe	Completed	Resolved
		• Hospitalization for small intestinal obstruction related to worsening constipation (no BM for 4-5 days prior), confirmed by CT scan. • Treatment consisted of restriction of oral intake, intravenous fluids, intravenous						

Treatment Arm	Subject ID	Verbatim AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
		antibiotics, ondansetron, acetaminophen, ketorolac, and bisacodyl. • The event (obstruction) resolved after the subject had a BM, confirmed on abdominal imaging (upper GI barium study with small bowel follow). <i>Reviewer comment: This GI-related SAE in a placebo patient represents a complication of the subject's underlying OIC.</i>						
	52339-008	Colitis	57/M	184	8	Severe	Withdrawn	Resolved
		• Hospitalization from Day 185 to 191 for nausea and vomiting diagnosed as colitis based on radiologic imaging • Medical history included obesity (BMI=31.6 kg/m ²) and diabetes mellitus type 2 • Findings on abdominal CT scan were reported to be consistent with colitis involving the mid-transverse colon to the sigmoid colon. • Treatment included intravenous hydration, magnesium sulfate, heparin, pantoprazole, levofloxacin, metronidazole, paracetamol, alprazolam, cefotetan, cyclobenzaprine, piperacillin/tazobactam, ondansetron, and prochlorperazine. • The study drug was withdrawn due to the event of colitis. <i>Reviewer comment: This GI-related SAE in a placebo patient is included for comparison to the study treatment arm. The subject's symptoms are similar to those with naldemedine-related GI effects, although the onset of the SAE occurred after long-term treatment. Details of CT findings were not provided, but it should be noted that thickening of the colon can be observed in patients with severe, chronic constipation.</i>						
	52399-007	Cholecystitis	58/F	300	2	Moderate	Withdrawn (non-AE)	Resolved
		• Hospitalization with abdominal pain secondary to cholecystitis, for which the subject underwent cholecystectomy. • Medical history was notable for BMI in the overweight range (29.8 kg/m ²) with history of obesity, cholelithiasis, hyperlipidemia, fibromyalgia, GERD, and menopause • The subject was withdrawn from the study due to a protocol violation unrelated to an adverse event <i>Reviewer comment: This GI-related SAE in a placebo patient is included for comparison to the study treatment arm. This event was not unexpected in this subject with prior history of cholelithiasis and multiple risk factors.</i>						
	52342-019	Flatulence	55/F	76	6	Severe	Withdrawn (Day 206, unrelated)	Resolved
		• Hospitalization for severe abdominal pain (Days 76 to 81) attributed to flatulence • Medical history included obesity (BMI=36.5 kg/m ²), diabetes mellitus type 2, GERD, kidney disease with renal stent, congestive heart failure, gout, hypertension, and sleep apnea. • Evaluation excluded pancreatitis (suspected diagnosis on admission) • Treatment included hydromorphone, ondansetron and lubiprostone. <i>Reviewer comment: This GI-related SAE in a placebo patient is included for comparison to the study treatment arm and likely represents symptoms of the</i>						

Treatment Arm	Subject ID	Verbatim AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
		<i>subject's underlying OIC.</i> <i>Of note, lubiprostone (one of the treatments provided to the subject) was a prohibited concomitant medication in Study V9235.</i>						
	52442-003	Vomiting	57/F	239 245 256	3 5 8	Moderate	Completed	Resolved
		- Multiple hospitalizations for vomiting (3 occurrences) during a 3-week period beginning on Day 239. - Medical history was notable for morbid obesity (BMI=40.1 kg/m²), diabetes mellitus type 2 with diabetic neuropathy, GERD, hyperlipidemia, and menopause. - Prior to the onset of vomiting, the subject was hospitalized from Day 230 to Day 236 for an abscess on the right great toe, for which the subject underwent an incision and drainage, and was treated with intravenous antibiotics, followed by oral antibiotic therapy with linezolid, continued after discharge from the hospital. - The first episode of vomiting was attributed to linezolid and resolved upon discontinuation. Intravenous vancomycin was started for ongoing treatment of her toe cellulitis. - The subject was re-admitted 4 days after discharge (Day 245 to Day 249) with vomiting, retching, loose stool, and non-cardiac chest pain. Decreased oral intake and urine output were recorded. Vancomycin was withheld, and the subject was treated with intravenous fluid hydration, acetaminophen, ondansetron, doxycycline, heparin, indomethacin, insulin, and pantoprazole. A myocardial perfusion stress test was performed during this admission which showed anteroseptal mild ischemia. - The subject was re-admitted from Day 256 to Day 263 for chest pain, abdominal pain, nausea, and vomiting (third occurrence). The subject's serum creatinine was noted to be elevated 1.26 (estimated glomerular filtration rate 53 mL/min). Treatment included intravenous antibiotics for the toe cellulitis (vancomycin and ceftaroline), docusate, insulin, nitroglycerin, pantoprazole, acetaminophen, ondansetron, and morphine. During this admission, the subject underwent transradial selective coronary angiography, left heart catheterization, and left ventriculography for unstable angina, which demonstrated no significant disease and preserved ventricular function. Renal function improved with hydration, and the subject was discharged on amoxicillin/clavulanate. <i>Reviewer comment: These GI-related SAE in a placebo patient are included for comparison to the study treatment arm. The events likely represent side effects of antibiotic therapy for the subject's preceding SAE of toe cellulitis.</i>						
	52448-002	Abdominal pain	48/F	43	11	Moderate	Withdrawn	Resolved
		- Hospitalization due to abdominal pain. - Medical history was notable for chronic abdominal pain. - Prior to admission the subject had been constipated for several days and then developed diarrhea with increased abdominal pain. - CT scan showed a colitis-like change extending from the proximal descending						

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Treatment Arm	Subject ID	Verbatim AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
		colon to the rectum which was noted by the colorectal surgeon to be more likely due to severe constipation than infectious colitis. • Treatment included dicycloverine hydrochloride, macrogol, and tramadol. • The subject discontinued the study drug on Day 43 as advised by study site personnel as the subject had stopped opioids on Day 26, and the subject was withdrawn from the study due to discontinuation of opioid medication. Reviewer comment: <i>This subject's symptoms (placebo) are similar to those with naldemedine-related GI effects and were considered by the investigator to be possibly related to study treatment. Therefore, it is notable that the onset of diarrhea and worsening abdominal pain occurred after discontinuation of opioids and may have represented GI withdrawal-type symptoms, though based on the reported inpatient treatment, the event may be due to underlying constipation.</i>						
	52449-001	Gastritis	53/F	244	10	Severe	Interrupted/ Lost to follow-up	Resolved
		• Hospitalization due to severe lower left abdominal pain of 1-week duration, diagnosed as gastritis. • During the hospital admission, a colonoscopy and endoscopy were performed, and an abdominal infection (unspecified) was diagnosed. • Treatment included pantoprazole and omeprazole. • The study drug was interrupted due to the event, and the subject was lost to follow-up after Study Day 266, though study treatment was reportedly resumed after hospital discharge on Day 253. Reviewer comment: <i>This GI-related SAE in a placebo patient is included for comparison to the study treatment arm.</i>						

(Source: Reviewer's table)

Table 72: SAEs of Opioid Overdose or Possible Opioid Overdose in Phase 3 Controlled Trials

Treatment Arm	Subject ID	AE Term	Age(yrs)/Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
Naldemedine (n=7)	22359-018	Overdose (opioid) <i>[fatal, presumed]</i>	37/F	9	N/A	Severe	N/A	Fatal
	<i>(Narrative is also found with deaths in Section 8.4.1)</i> - This fatal SAE (cardiopulmonary arrest) was presumed to be caused by an overdose of opioid medication, including methadone [no supporting toxicology data] - Medical history included prior methadone overdose, obesity (BMI=32.1 kg/m²), anxiety, attention deficit hyperactivity disorder, bipolar disorder/depression, degenerative disc disease, osteoarthritis, headaches, hypertension, IUD placement (levonorgestrel-containing), and peripheral neuropathy. - The subject was found pulseless and apneic after an unwitnessed event; naloxone was administered and cardiopulmonary resuscitation (CPR) was initiated, including intubation and administration of epinephrine, atropine, norepinephrine, and sodium bicarbonate - Further care was withheld after head CT showed cerebral edema consistent with global anoxia - An autopsy was not performed. <i>Reviewer comment: Presumptive diagnosis of overdose without any supportive clinical data or post-mortem evaluation (only prior history of overdose)</i>							
	52306-010	Overdose/ Toxic encephalopathy	66/M	82	1	Severe	Withdrawn (unrelated)	Resolved
- The subject was admitted to the hospital due to altered level of consciousness due to possible overdose of methadone (for chronic knee and back pain) and unspecified benzodiazepines. - Medical history included obesity (BMI=31.1 kg/m²) - Notable findings on evaluation included urine drug screen positive for benzodiazepines and <u>negative for opiates</u>; elevated myoglobin (attributed to trauma from fall), normal CK-MB and troponin levels; and head CT without acute process - Treatment included naloxone and flumazenil. - Study treatment was discontinued on Day 89 due to a protocol violation of gastric bypass (eligibility violation), which was unrelated to this SAE. <i>Reviewer comment: SAE attributed to possible methadone overdose event though urine drug screen was negative for opiates.</i>								
	52327-	Overdose	51/M	378	9 (see comment)	Severe	Completed	Resolved

Treatment Arm	Subject ID	AE Term	Age(yrs)/Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
	031	- The subject was found with altered level of consciousness and noted to be pale and diaphoretic; on presentation to the hospital, the subject was also noted to have hypotension and acute kidney injury - Medical history included chronic kidney disease stage 3, chronic back pain, Gout, hypertension, overweight, peripheral neuropathy; also with history of chronic narcotic dependence and hematochezia not reported to the study site prior to this SAE - Evaluation was notable for BP 88/57 (unresponsive to fluid bolus), creatinine 4.2 mg/dL (prior level 2.1 mg/dL), AST 111 units/L, and ALT 46 units/L; of note, hemoglobin was normal (12.5 g/dL), and urinalysis was “consistent with UTI”, but urine culture was negative. - After administration of naloxone, the subject became awake, alert, and “somewhat agitated”; and BP was improved. - The subject reported to have donated plasma earlier in the day, and denied taking extra/higher doses of pain medication - Inpatient treatment consisted of aggressive hydration with resolution of hypotension and improvement in creatinine to 1.4 mg/dL; the subject also underwent a colonoscopy due to the subject’s report of “hematochezia for several years”, which demonstrated multiple ulcers in the proximal ascending colon and cecum (one with active bleeding requiring hemostasis clips and one with fibropurulent material and acute inflammation), suspected to be due to NSAID treatment. - In addition to the diagnosis of “suspected narcotic overdose”, the subject also received diagnoses of hypotension due to dehydration, heat exhaustion, and acute kidney injury related to pre-renal azotemia (all included under this SAE of “overdose”). <i>Reviewer comment: This subject raises concern for risk of overdose following naldemedine administration, although in this case, the accumulation of opioids was likely due to acute decline in renal function due to pre-renal azotemia in a subject with underlying renal impairment. The contribution of naldemedine treatment to the development and/or severity of this event cannot be determined. GI toxicity would represent a risk factor for development of pre-renal azotemia, though etiology for the subject’s pre-renal azotemia is not clear from the available data or SAE narrative.</i> <i>*This duration of this SAE was reported to be 9 days; however, the narrative indicates that the AE of overdose was resolved on the same day as onset with normalization of mental status. The hospitalization was prolonged due to acute kidney injury and evaluation of hematochezia, which revealed large intestinal ulcerations, likely due to chronic NSAID use (which could also have led to reduction in renal function), and less likely to be the result of naldemedine treatment.</i> <i>This event occurred concurrently with end of study treatment. The elevated AST level >5 times the upper limit during hospitalization was not included among study laboratory data, and therefore, not included as a liver event. No follow-up level was obtained because this abnormality was not identified as treatment-emergent transaminase abnormality.</i>						
	52364-006	Overdose	51/F	75	2	Severe	Completed	Resolved
		Hospitalization for “disturbance of consciousness” due to accidental opioid overdose						

Treatment Arm	Subject ID	AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
		(morphine and hydrocodone) • Medical history included bipolar disorder/depression, renal insufficiency, chronic back pain, COPD, migraine, hypothyroidism, and obesity (BMI=38.5 kg/m ²). • Naloxone was administered for treatment of overdose						
	52368-028	Toxic Encephalopathy	65/F	155	1	Severe	Withdrawn (unrelated)	Resolved
		• Hospitalization for toxic encephalopathy (acute confusion, agitation, and disorientation to time) attributed to long-acting opioids (oxycodone and hydrocodone) and benzodiazepines (alprazolam). • Medical history included morbid obesity (BMI=58.1 kg/m ²), anxiety, atrial fibrillation, asthma, chronic pain (foot, knee, back, hip), degenerative disc disease, bilateral knee replacement, spinal fusion, hypertension, migraines, sciatica, • Evaluation was notable for head CT with no acute abnormalities and changes of chronic small vessel ischemia (moderate diffuse deep white matter disease), chest X-ray revealed mild congestive heart failure, urine culture positive for Escherichia coli. • Opioid doses were reduced and alprazolam was discontinued. No administration of naloxone was reported. • The subject was subsequently withdrawn from the study on Day 189 due to non-compliance with study medication and visit schedule. The last reported dose of study drug was Day 182. <i>Reviewer Comment: In patient diagnostic evaluation was notable for a positive urine culture with E.coli. The subject's symptoms could have been attributable to an active urinary tract infection (UTI); however, the urine culture result was the only reference to a possible UTI in the narrative.</i>						
	52381-006	Loss of Consciousness	63/M	180	1	Moderate	Withdrawn	Resolved
		• Hospitalization due to loss of consciousness after being found unresponsive on the floor by a family member. • The subject reportedly regained consciousness that same day. No other information, including medications administered, was available because the Applicant was unable to obtain the subject's hospital records despite several reported attempts. • The last reported dose of study drug was Day 180, after which the subject withdrew consent for study participation. <i>Reviewer Comment: There was insufficient information for this SAE determine the nature or etiology of this event.</i>						
	52401-015	Post-operative respiratory failure	52/F	202	7	Severe	Completed	Resolved
		• The subject developed prolonged post-operative acute respiratory failure (duration 7 days) after surgery for osteoarthritis and degenerative disc disease of the spine • Medical history included morbid obesity (BMI = 65.2 kg/m ²), COPD, asthma, hypothyroidism, multiple episodes of pneumonia, and history of spontaneous pneumothorax. • No information regarding the onset, progression, management, or associated symptoms of this SAE was provided.						

Treatment Arm	Subject ID	AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
		Reviewer's comment: This event differs from the others in this table because the onset of the SAE occurred while the subject was an inpatient during the post-operative period. Although this subject had multiple risk factors for post-operative respiratory failure (morbid obesity, COPD), in addition to chronic opioid use, this case has been presented in this table the possibility of opioid-mediated respiratory depression with administration of acutely higher doses of opioid medication due to reduced effectiveness of opioid analgesia by naldemedine cannot be excluded. However, this reviewer acknowledges that this SAE was unlikely caused by opioid overdose alone. No use of centrally-acting opioid antagonists was reported in the narrative or concomitant medication dataset.						
Placebo (n=5)	12328-003	Overdose	55/F	40	4	Moderate	Completed	Resolved
		- The subject presented with confusion and decreased oxygen saturation secondary to medication overdose (multi-drug, including opioid medication), reported to be accidental - Medical history included multiple sclerosis, arthritis, neck pain, fibromyalgia, post-traumatic stress disorder, migraines, anxiety, depression, hypertension, and COPD. - The medications involved in the overdose were controlled-release morphine, amitriptyline, and lorazepam. - No additional information regarding evaluation or management was provided. Reviewer's comment: This event in a placebo subject demonstrates the high background risk of polypharmacy and related complications in this study population.						
	22324-008	Syncope	44/M	19	3	Severe	Withdrawn	Resolved
		(This SAE is also described in Section 8.5.3 due to the co-occurrence of MACE (MI type 2)) - Hospitalization with hypotension after a syncopal episode with a 2- to 3-day history of altered mental status, weakness/confusion, weakness, and somnolence; and multiple falls also noted within the several days prior. Rectal bleeding was also noted around the same time (onset unclear). - Medical history included anxiety, obesity (BMI = 34.2 kg/m²), arthritis, intervertebral disc herniation, cervical spinal stenosis/cervicalgia, fibromyalgia, recurrent bronchitis and sinusitis, frequent falls, headaches, histoplasmosis, hypertension, multiple orthopedic surgeries, intermittent rectal bleeding, muscle spasms, tobacco use, and weakness - Hypotension and altered mental status improved after naloxone and intravenous fluids. - The SAE of syncope (with mental status changes) was considered possibly related to subject's medications, which included oxycodone and alprazolam, as well as citalopram, amitriptyline, tizanidine, pregabalin, and lisinopril. - This event (admission) was associated with multiple related diagnoses, including hypotension, acute kidney injury, and nontraumatic rhabdomyolysis. In addition, the subject's ECG showed sinus tachycardia with inverted T waves and ST segment depression, which the CAC adjudicated as a myocardial infarction, type 2 (MACE). - The subject had discontinued study treatment 4 days prior to SAE onset, reportedly due to severe rectal bleeding						

Treatment Arm	Subject ID	AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
		Reviewer's comment: This extremely complicated event of "syncope" represents an event of hypovolemia/hypotension with hypoperfusion resulting in cardiac ischemia, adjudicated as MACE by the CAC, also with acute renal injury due to pre-renal azotemia and possible additional injury secondary to rhabdomyolysis. This series of events in a placebo subject demonstrates a case of secondary myocardial ischemia in the absence of δ-opioid antagonism by PAMORA treatment.						
	22348-002	Mental Status Changes (Sick Sinus Syndrome)	59/F	77	2	Moderate	Interrupted/Completed	Resolved
		- Hospitalization from Day 78 to Day 83) for mental status changes, presenting with reported symptoms of slurred speech and difficulty with coordination), which were considered possibly due polypharmacy (oxycodone, butalbital/acetaminophen/caffeine), duloxetine, bupropion, tizanidine, topiramate, ropinirole, zolpidem); sick sinus syndrome (SSS) was the other proposed etiology for the subject's symptoms. - Medical history included transient ischemic attack, chronic back pain, insomnia, migraine, and overweight (BMI = 29.7 kg/m²) - Evaluation for CVA was negative; sick sinus syndrome was diagnosed with pacemaker placement on Day 83 (Hospital day 6), though the SAE of mental status changes was considered resolved on Day 78 (Hospital Day 1, SAE Day 2) - The study drug was interrupted from Day 79 until Day 86 due to the event Reviewer's comment: This SAE in a placebo-treated subject is included for comparison to study treatment						
	52352-002	Overdose [fatal, presumed]	52/M	50	N/A	Severe	N/A	Fatal
		(Narrative is also found with deaths in Section 8.4.1) - This fatal SAE (cardiopulmonary arrest) was presumed to be caused by an accidental overdose of opioid medication [no supporting toxicology data] - Medical history included diabetes mellitus type 2, overweight (BMI=28.1 kg/m²), back pain, prior back surgery, and peripheral neuropathy - The coroner's report listed the cause of death as "overdose", based solely on the family's report of the subject's opioid use; an autopsy was not performed and no supportive laboratory data were obtained. - The last known dose of study medication is unknown; subject missed the scheduled study Visit 5. The site attempted to contact the subject on that same day, unsuccessfully. Reviewer comment: Presumptive diagnosis of overdose without any supportive clinical data or post-mortem evaluation (only prior history of overdose)						
	52400-010	Mental status change Respiratory failure	53/F	350	2	Severe	Completed	Resolved
		- Hospitalization altered mental status and acute respiratory failure (hypoventilation) attributed to polypharmacy (fentanyl, oxycodone, tramadol, gabapentin, duloxetine, cyclobenzaprine), exacerbated by obesity-related hypoventilation; the subject presented after falling at home, resulting in a wrist fracture. - Medical history included morbid obesity (BMI=42.3 kg/m²), anxiety, depression,						

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Treatment Arm	Subject ID	AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
		transient ischemic attack, back pain, meniscal tear, and chondromalacia of the knee. Naloxone was administered; other treatment included bilevel positive airway pressure (BiPAP) and withholding of suspected causative medications Reviewer's comment: <i>This SAE in a placebo-treated subject is included for comparison to study treatment</i>						

The following table contains the narratives for the additional 14 SAEs of interest in subjects treated with naldemedine in placebo-controlled, phase 3 clinical trials, as listed above

Table 73: Additional SAEs of Interest in Phase 3 Placebo-Controlled Trials (n=13)

Subject ID	AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
10602-002	Allergic Reaction	55/F	1	1	Moderate	Withdrawn	Resolved
	- Onset of hypersensitivity reaction within 2 hours after administration of 1st dose - Symptoms of diarrhea and vomiting, followed by bronchospasm and dyspnea (treated in ER due to respiratory symptoms and persistence of GI symptoms) - Elevated BP (177/96) and HR (106), no hypotension or hypoxia reported - Evaluation notable for bilateral wheezing and leukocytosis (20.1/mm³); also reported slight elevations of CRP, transaminases, and glucose (no results) - Prior medical history includes GI conditions of diverticulosis, hiatal hernia, and gastric ulcer disease; respiratory conditions of asthma, pneumonia, and pulmonary embolism; allergies to penicillin, doxycycline, tetracycline, iodine, benzododecinium bromide (topical antiseptic), and adhesive, with history of anaphylactic shock to general anesthesia; environmental allergies (pollen, dust mites, bee stings) - Treatment with promethazine, omeprazole, and metoclopramide for vomiting; and fenoterol and anbroxol for wheezing Reviewer comment: <i>This SAE is consistent with a treatment-related hypersensitivity reaction that meets clinical criteria for anaphylaxis due to the concurrent (1) presence of respiratory compromise and (2) persistent gastrointestinal symptoms, occurring rapidly after exposure (minutes to several hours) [Sampson 2006]. While the subject's GI symptoms are consistent with other naldemedine GI reactions, and vomiting could have triggered bronchospasm, the co-occurrence of bronchospasm is suggestive of a hypersensitivity reaction. The subject's medical history would support either scenario, and this reviewer notes that treatment with antihistamines or corticosteroids were not reported. Therefore, in absence of cutaneous manifestations or hypotension, this reviewer considers this SAE to be a likely hypersensitivity reaction, possibly anaphylaxis.</i>						
12302-011	PVCs in Triplets	64/F	52	37	Moderate	Interrupted/ Completed	Resolved
	- Onset of unifocal premature ventricular contractions (PVCs) in triplets and elevated BP after administration of anesthesia (propofol, fentanyl, midazolam, and ketamine) during an outpatient procedure (blepharoplasty), for which the subject's atenolol had been held - Prior medical history was notable for paroxysmal supraventricular tachycardia post ablation, hypertension, type 2 diabetes, obesity, sleep apnea, and cardiomegaly - ECG showed occasional PVCs, ST abnormality, and possible digitalis effect; occasional						

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Subject ID	AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
	episodes of PVCs (asymptomatic) were noted during inpatient observation • Study drug treatment was interrupted on Day 52 and resumed on Day 54. <i>Reviewer comment: This reviewer agrees with the Investigator's assessment that the PVCs can likely be attributed to withholding of beta blocker therapy with possible contribution by anesthetic medication(s). A causal role of naldemedine treatment is considered less likely.</i>						
12322-008	Supraventricular tachycardia	65/F	18	7	Severe	Withdrawn	Resolved
	• Hospitalization on Day 18 with SVT and elevated blood pressure (203/90) • Presented with complaints of chest pressure, chest pain, nausea, and emesis • Serum troponin and B-type natriuretic peptide levels were elevated • ECG showed SVT and pronounced ST segment depression in 1 lead. • SVT was initially treated with amiodarone and enoxaparin; intravenous adenosine was given upon recurrence of SVT and metoprolol was started • Study drug was withdrawn on Day 29 due to the event; • ECG at Early Termination Visit was considered "borderline" (sinus rhythm with sinus arrhythmia, first degree atrioventricular block, and low voltage QRS) • The event was adjudicated by the CAC as a MACE (AMI, type 2) <i>Reviewer comment: This event was considered possibly due to study treatment, and the CAC concluded that this subject experienced cardiac ischemia secondary to SVT, consistent with an MI type 2. Any causal role of naldemedine in either the cardiac arrhythmia or ischemia is not known. However, treatment was discontinued due to this SAE without treatment rechallenge.</i>						
12333-005	COPD exacerbation	61/F	25 39	3	Severe	Completed	Resolved
	• Hospitalizations (2 events in <1 month) for COPD exacerbation (pre-existing condition), presenting with respiratory distress • Hypertensive emergency diagnosed on first hospital admission • Prior medical history was also notable for cardiac bypass (quadruple), hypertension, diabetes, Wilson disease, chronic edema, morbid obesity, congestive heart failure, coronary and peripheral artery disease. Home medications included ipratropium bromide, Advair, albuterol, montelukast, furosemide, and home oxygen therapy. • During the first hospitalization (Day 25-27), the subject had elevated cardiac enzyme levels that improved with blood pressure control; treatment included corticosteroids, diuretics, oxygen therapy, nebulizer treatments, and antibiotics (doxycycline) as well as morphine for dyspnea; the subject was discharged on hospital day 3 on a prednisone taper regimen, bumetanide, nebulizer treatments, and oxygen. • The subject was re-admitted from Day 39 (12 days after discharge) to Day 43 with acutely worsening dyspnea, oxygen saturation <90%, and chest pain; cardiac enzymes were again elevated, ECG revealed sinus rhythm with premature ventricular complexes, marked ST abnormality, and T-wave abnormalities; nuclear stress test was worrisome for ischemia and decreased left ventricular ejection fraction (46%). The cardiology consultant diagnosed acute-on-chronic diastolic CHF. • The second hospital course was notable for hypertensive urgency/emergency and worsening fluid overload with congestive heart failure; treatments included antihypertensives, diuretics, intravenous corticosteroids, sodium restriction, inhaled albuterol/ipratropium, oxygen,						

Subject ID	AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
	antibiotics, and morphine. • The event was adjudicated as a noncardiovascular event by the CAC <i>Reviewer comment: These events of COPD exacerbation, accompanied by hypertensive urgency/emergency and CHF, are not unexpected in this subject with a pre-existing diagnosis of COPD and numerous risk factors. Although the co-occurrence of COPD exacerbation and CHF with diastolic dysfunction, this SAE was identified due to its complicated nature. Any effect of opioid receptor antagonism on the severity and persistence of CHF, leading to exacerbation of respiratory distress cannot be determined. Since opioids, particularly morphine used for treatment of CHF due to their vasodilatory effects [REF] and is currently the subject of academic studies, including a large scale clinical trial comparing morphine and fentanyl in acute pulmonary edema, the potential effects of opioid antagonism needs to be considered.</i>						
50409-006	Congestive heart failure	54/F	51 131	5 27	Severe	Withdrawn	Resolved
	• Hospitalizations (2 events) for congestive heart failure • Medical history included morbid obesity (BMI=51.5 kg/m²), diabetes mellitus type 2, myocardial infarction, atrial fibrillation, pacemaker placement, chronic kidney disease, COPD, hypertension, peripheral artery disease, chronic back pain, hyperlipidemia, hypothyroidism, postmenopausal, panic attacks. • The subject initially presented with worsening edema unresponsive to outpatient diuretic management and was admitted from Day 51 to Day 55, during which management consisted of diuretics, insulin titration, and fluid/sodium restriction. • The subject presented on Day 131 with confusion, shortness of breath, and orthopnea, for which she hospitalized from Day 132 until Day 157. • On presentation, the subject was noted to have renal failure (GFR 12), and her significantly depressed level of consciousness was attributed to accumulation of opioids and pregabalin, in the setting of acute kidney injury. • Management included adjustments of opioids, including discontinuation of long-acting medications, hemodialysis (ultrafiltration for fluid removal), and intravenous antibiotics for chronically weeping lower extremity wounds. • GFR returned to baseline (57 mL/min) after approximately 2 weeks • The last dose of the study drug was on Day 163. The subject was withdrawn from the study by the investigator due to unblinding by the CRO. <i>Reviewer note: These events of CHE exacerbation are not unexpected in this subject with relevant prior medical history and risk factors. However, this event was identified as notable due to the recurrence of symptoms leading to unblinding by the CRO. See the reviewer comment for Subject 12333-005.</i>						
50709-005	Sinus tachycardia	43/F	337	3	Moderate	Completed	Resolved
	• Hospitalization from Day 337 to Day 339 for tachycardia and dyspnea starting on Day 335. • Medical history included asthma, fibromyalgia, migraine, recurrent sinusitis, depression, and endometriosis, • Prior to the onset of tachycardia and dyspnea, the subject also had a 1-day history of fever and fatigue • Evaluation was notable for BP 147/108, pulse 126 (beats per minute), ECG with sinus						

Subject ID	AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
	tachycardia and nonspecific T-abnormality; spirometry was normal. • Treatment included budesonide, montelukast, and guaifenesin/terbutaline for a diagnosis of asthma <i>Reviewer comment: The etiology of this subject's tachycardia is not clear; however, a relationship with study treatment is unlikely given the late onset of the event and lack of prior vital sign abnormalities.</i>						
52325-016	Hepatitis	63/F	253	109	Moderate	Withdrawn	Resolved
	(discussed in section 9.4.7, Liver Events) <i>Reviewer comment: This event is included because it represents the only SAE consistent with drug toxicity and led to study drug discontinuation; however, verapamil was ultimately determined to be the causal agent.</i>						
52331-005	Stress	53/F	6	102	Moderate	Withdrawn (unrelated)	Resolved
	• The subject experienced a disabling/incapacitating event of "stress" (the subject was unable to work). • Medical history included morbid obesity (BMI=40.3 kg/m ²), cephalgia, chronic back pain, fibromyalgia, hypertension, hypothyroidism, kidney failure, spinal osteoarthritis, postmenopausal, and sleep apnea. • The SAE of stress was occurred from Study Day 6 to 107. • No treatment medication was provided for the SAE of stress, but the subject was prescribed time off from work. • Later in the treatment period, the subject was withdrawn from the study (last dose Day 293) due to incorrect medication dosing (subject took 2 pills instead of 1 due to perceived increased efficacy). The subject's noncompliance was noted on Day 107 and persisted despite counseling by the investigator's staff. Incorrect drug dosing was considered unrelated to the SAE. <i>Reviewer comment: Symptoms of agitation, anxiety, nervousness are the neurological symptoms which may occur with opioid withdrawal. Given the early onset and prolonged duration of this SAE of "stress", an effect of study treatment cannot be excluded. On the other hand, TEAEs of anxiety, panic, attack, agitation, etc., did not occur more frequently in the treatment arm. (See Section 8.4.5) This reviewer notes the relatively high prevalence of pre-existing mood disorders in this study population.</i>						
52334-017	Skin necrosis, Peripheral arterial occlusive disease	55/M	273 274	4	Moderate	Interrupted/ Completed	Resolved
	• Hospitalization for skin necrosis from Day 274 to Day 281 at the site of an ulcer on the left ankle that developed on Day 254 after left ankle replacement on Day 220. • Medical history included obesity (BMI=31.8 kg/m ²), diabetes mellitus type 2, anxiety, GERD, gout, back pain, hypercholesterolemia, hypertension, erectile dysfunction, low testosterone, peripheral neuropathy, multiple fractures, and degenerative joint disease. • Diagnostic evaluation included CT angiogram of the abdominal aorta which showed left lower extremity occlusion. • Treatment initially included antibiotics, multiple debridements, wound care, and pain						

Subject ID	AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
	management, and the subject underwent left distal femoral to peroneal artery bypass on Day 277. • Study treatment was reportedly interrupted for an unspecified time period during this event. Reviewer comment:						
52349-008	Femoral artery occlusion	55/F	225	60	Moderate	Completed	Resolved
	• Hospitalization for peripheral vascular disease with femoral artery occlusion. • Medical history included prior acute myocardial infarction, coronary angioplasty, systemic lupus erythematosus, anemia, chronic back pain, degenerative joint disease (knees), GERD, hyperlipidemia, hypertension, post-menopausal, repaired aortic aneurysm, and overweight (BMI=27.4 kg/m ²). • The subject had been diagnosed on Day 220 with a non-serious AE of peripheral vascular disorder/disease which did not resolve, and the subject presented 5 days later with a femoral artery occlusion for which she underwent femoropopliteal bypass surgery to the right leg on Day 284. • Non-surgical treatment included cefazolin, heparin sodium, nitroprusside, nicardipine, fentanyl, and labetalol. • The subject was also diagnosed with an aortic aneurysm on Day 228, considered a non-serious AE. Reviewer comment: <i>This SAE is one of the peripheral vascular events that raise concern for naldemedine treatment. Peripheral vascular disease is common in this high-risk population. These events are not sufficient to suggest a causal role in the development of these events. Routine post-marketing surveillance is recommended to assess for treatment-related risk.</i>						
52362-021	Sickle cell anemia with crisis	56/F	4	4	Severe	Lost to follow-up	Resolved
	• Hospitalization for sickle cell crisis/vasoocclusive crisis, presenting with lower back pain, left hip pain, and left knee pain. • Medical history • Treatment included intravenous fluids, hydromorphone, ketorolac, and lorazepam. • The subject was lost-to follow-up, and the last day of exposure to study drug was Day 41. Reviewer comment: <i>This subject was the only subject in naldemedine phase 3 clinical trials with sickle cell anemia. Early onset of vasoocclusive crisis following initiation of naldemedine treatment and discontinuation of study treatment shortly thereafter (subject lost to follow-up) suggests that naldemedine may not be well-tolerated in this population. Minimal data also exist for the other PAMORAs. Insufficient data are available to conduct an assessment of safety for the entire sickle cell patient population and may warrant evaluation.</i>						
52415-004	Pulmonary embolism DVT Myocardial infarction Adenocarcinoma	52/F	2	N/A	Severe	Withdrawn	Fatal
	Hospitalization for chest pain and dyspnea, diagnosed with adenocarcinoma but also found						

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Subject ID	AE Term	Age(yrs)/ Sex	Onset (day)	Duration (days)	Severity	Disposition	Outcome
	to have DVT with pulmonary embolism and cardiac ischemia, diagnosed with myocardial infarction by cardiac catheterization. <i>Reviewer comment: This group of co-occurring SAEs is referenced multiple times in this review. This subject has been included in this table because this subject and the next subject in this table (Subject 52428-007) are the only subjects with pulmonary embolism in the phase 3, placebo-controlled safety population. In this case, the subject's malignancy places the subject at substantial risk for thrombosis. These 2 subjects, along with other treatment emergent thrombotic events and data from other PAMORAs, are not sufficient to suggest an increased risk with naldemedine.</i>						
52428-007	Pulmonary embolism Pneumonia	56/M	356	Unknown	Severe	Completed	Not recovered
	• Hospitalization for pneumonia and bilateral pulmonary emboli (Day 356) presenting with dyspnea, cough, and hypoxia. • Medical History: Parkinsons disease, Parkinson-related dementia, COPD, myocardial infarction, migraines, arthritis, lower extremity edema, cervical dystonia, chronic back pain, chronic sinusitis, GERD, depression, anxiety, hyperlipidemia, fainting episodes, and overweight (BMI=29.7 kg/m²). • The subject presented with somnolence, decreased responsiveness, and fever. The subject's care taker reported trouble swallowing pills, poor oral intake, decreased, and 20-lb weight over the prior week. • Evaluation was notable for oxygen saturation of 72%; ECG with sinus tachycardia, possible left atrial enlargement, incomplete right bundle branch block, and a nonspecific T-wave abnormality; CT scan of the chest with bilateral pulmonary emboli, bilateral patchy ground glass and consolidative opacities, and mediastinal lymphadenopathy • Treatment included anticoagulation (enoxaparin and warfarin). • The subject was discharged on Day 365 but re-admitted on Day 372 for overnight observation for hemoptysis • At last follow-up, no information was available on the status of the subject's recovery from the pulmonary embolism and pneumonia. <i>Reviewer comment: This subject and the previous subject in the table (Subject 52415-004) are the only 2 subjects with pulmonary embolism in the phase 3, placebo-controlled safety population. These data are not sufficient to consider the possibility of a thrombotic safety signal for this drug. Routine post-marketing surveillance is recommended for further assessment of risk.</i>						

(Source: Reviewer's table)

Post-treatment, treatment-emergent SAEs

Although delayed treatment-related adverse effects would not be expected with after discontinuation of naldemedine and has not been reported with this drug class, the long-term effects of these drugs are not fully known. Overall, a review of TEAEs occurring >5 days after treatment discontinuation, as well as AEs with onset after Day 14 of the follow-up period, did not identify any new safety concerns. However, the following 3 treatment-emergent SAEs in the

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naldemedine arm with onset >5 days after discontinuation are considered events of interest based on the safety concerns for this medication class.

- 12333-025: Deep venous thrombosis (moderate, resolving)-58 year-old female experienced an SAE deep vein thrombosis (DVT) of the right leg with acute onset of symptoms on Day 23 of the 28-day follow-up period (Study Day 107).
- 12351-008: Transient ischemic attack (mild, resolved)- 74 year-old female with history of seizure disorder and prior gunshot to the frontal lobe experienced an SAE of transient ischemic attack (TIA) on Day 14 of the 28-day follow-up period (Study Day 102). The subject reported feeling disoriented, agitated, and confused while at an orthopedic visit. Symptoms reported during hospitalization included headache, memory loss, dizziness, lightheadedness, blurred vision, general weakness, and a raspy voice. On evaluation, the subject was awake, alert, and oriented; vital signs were notable for a BP of 160/70 mmHg, and ECG showed right bundle branch block and nonspecific ST changes. Head CT showed no obvious mass or hemorrhage, but the study was limited due to extreme artifact due to left frontal cranioplasty and focal metallic fragment in the right frontal lobe. Similarly, CT angiogram of head and neck showed no significant arterial stenosis, vascular occlusion, thrombosis, or aneurysm, but was limited by artifact. The consulting neurologist considered the event to be consistent with a possible complex headache. Symptoms improved within 24 hours, and the subject was discharged from the hospital on continued treatment with carbamazepine. The event was adjudicated as a non-cardiovascular event by the CAC.
- Subject 22321-018: ischemic colitis (moderate, resolved)- 56 year-old female was admitted to the hospital on Day 61 (29 days after study drug discontinuation) with diagnosis of possible ischemic colitis. The subject presented with ‘stringy diarrhea with blood’, associated with sharp, stabbing left lower quadrant abdominal pain, following passage of hard stool. Biopsy of right colon and rectum was normal. Colonoscopy revealed acute mild to moderate inflammation located 25 to 35 cm from the anal verge and appeared related to ischemic colitis or infectious colitis, and CT of the abdomen showed significant decompression of the sigmoid colon.

The study drug was discontinued on Study Day 32 due to a treatment-emergent SAE of lymphadenopathy. The subject presented at that time with tachycardia, sweating, and flushing. CT scan showed multiple and hilar lymph nodes were also noted multiple pulmonary nodules/lesions; and thoracic, mediastinal, and hilar lymphadenopathy. It was reported that differential diagnoses of cancer, sarcoidosis, lymphoma, and metastatic lung cancer were all ruled out.

The event of “ischemic colitis” occurred in the context of OIC after study drug discontinuation and was reported to be a diagnosis of exclusion. There was no evidence of vascular compromise.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Events

In the pooled phase 3 safety population, 75 subjects in the naldemedine group had a premature study termination attributed to a TEAE (6.4%), vs. 53 subjects in the placebo group (4.5%). One additional subject in the naldemedine withdrew due to an AE identified prior to study drug administration (i.e., not a TEAE). AEs leading to study discontinuation are summarized in Table 72.

The AEs leading to early study termination have been divided into subgroups of GI AE, events of opioid withdrawal (OW), pain-related AE, and “other” AEs that do not fit into one of the other categories. Subjects with both OW and GI events were categorized only in the OW group. Pain-related events only included those whose verbatim terms directly cited increased pain or reduced opioid efficacy as the cause of discontinuation. Consistent with the overall safety profile of this drug, GI AEs were largest subgroup of discontinuations among naldemedine-treated subjects. In the placebo arm, the “other” subgroup was the largest group of AEs leading to study discontinuation. This difference between treatment groups supports a causal relationship between GI events and study treatment. In the pooled Phase 3 safety population, 3.2% of naldemedine-treated subjects withdrew enrollment due to GI events, compared to 1.5% of placebo-treated subjects. Within the subgroup of GI events, the 4 main GI symptoms of naldemedine toxicity (abdominal pain, diarrhea, nausea, and vomiting) accounted for all GI-related study discontinuations in the naldemedine arm (n=37), vs. 13 of 17 GI-related discontinuations in the placebo arm. GI reactions due to naldemedine treatment are discussed in detail in Section 8.4.4.

Table 74: TEAEs leading to Study Discontinuation

AE Type	V9231 and V9232 (12-Week Studies)		V9235 (52-Week Study)		Overall	
	Naldemedine (N=542)	Placebo (N=546)	Naldemedine (N=621)	Placebo (N=619)	Naldemedine (N=1163)	Placebo (N=1165)
ANY AE	30 (5.5)	17 (3.1)	45 (7.2)	36 (5.8)	75 (6.4)	53 (4.5)
GI	16 (3.0)	9 (1.6)	21 (3.9)	8 (1.3)	37 (3.2)	17 (1.5)
Any GI						
Abdominal pain, diarrhea, nausea, vomiting*	16 (3.0)	7 (1.3)	21 (3.9)	6 (1.0)	37 (3.2)	13 (1.1)
Anal Fissure	0	1 (0.2)	0	0	0	1 (0.1)
Colitis	0	0	0	1 (0.2)	0	1 (0.1)
Diverticulitis	0	0	0	1 (0.2)	0	1 (0.1)
Hematochezia**	0	1 (0.2)	0	0	0	1 (0.1)
OW	4 (0.7)	1 (0.2)	5 (0.8)	4 (0.6)	9 (7.7)	5 (0.4)
Any OW-related						
OW per PI*	1 (0.2)	1 (0.2)	3 (0.4)	3 (0.4)	4 (0.3)	4 (0.3)
Possible OW, both GI/non-GI	3 (0.6)	0	1 (0.2)	1 (0.2)	4 (0.3)	1 (0.1)
Possible OW, GI only	0	0	1 (0.2)	0	1 (0.1)	0
Pain	2 (0.4)	0	4 (0.6)	4 (0.6)	6 (0.5)	4 (0.3)
Other	8 (1.5)	7 (1.3)	15 (2.4)	20 (3.2)	23 (2.0)	27 (2.3)
Any Other						
Abnormal Transaminase(s)	3 (0.6)	0	3 (0.4)	6 (1.0)	6 (0.5)	6 (0.5)
Malignancy/Suspected	1 (0.2)	2 (0.4)	2 (0.3)	2 (0.3)	3 (0.3)	4 (0.3)
Renal impairment	0	0	1 (0.2)	2 (0.3)	1 (0.1)	2 (0.2)
Cellulitis	0	0	0	2 (0.3)	0	2 (0.2)
Edema Peripheral	0	1 (0.2)	1 (0.2)	0	1 (0.1)	1 (0.1)
Anemia	0	0	0	1 (0.2)	0	1 (0.1)
AV Block	0	0	0	1 (0.2)	0	1 (0.1)
Chills, Anxiety	0	0	0	1 (0.2)	0	1 (0.1)
CIDP, worsening	0	1 (0.2)	0	0	0	1 (0.1)

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AE Type	V9231 and V9232 (12-Week Studies)		V9235 (52-Week Study)		Overall	
	Naldemedine (N=542)	Placebo (N=546)	Naldemedine (N=621)	Placebo (N=619)	Naldemedine (N=1163)	Placebo (N=1165)
Congestive heart failure	1 (0.2)	0	0	0	1 (0.1)	0
COPD exacerbation	0	1 (0.2)	0	0	0	1 (0.1)1
DVT/Pulmonary embolism	0	0	1 (0.2)	0	1 (0.1)	0
Headache	0	0	0	1 (0.2)	0	1 (0.1)
Hyperglycemia	0	0	1 (0.2)	0	1 (0.1)	0
Hypersensitivity	1 (0.2)	0	0	0	1 (0.1)	0
Insomnia	0	0	1 (0.2)	0	1 (0.1)	0
Leukocytosis	0	0	0	1 (0.2)	0	1 (0.1)
Muscle spasms, generalized	0	0	1 (0.2)	0	1 (0.1)	0
Myocardial infarction	0	0	0	1 (0.2)	0	1 (0.1)
Necrotizing fasciitis	0	0	0	1 (0.2)	0	1 (0.1)
Paralysis, lower extremities	1 (0.2)	0	0	0	1 (0.1)	0
Patella fracture	0	0	0	1 (0.2)	0	1 (0.1)
Photosensitivity	0	0	1 (0.2)	0	1 (0.1)	0
Pneumonia	0	1 (0.2)	0	0	0	1 (0.1)
Prolonged INR	0	1 (0.2)	0	0	0	1 (0.1)
Psychosis, acute	0	0	1 (0.2)	0	1 (0.1)	0
Rash	0	0	1 (0.2)	0	1 (0.1)	0
Supraventricular tachycardia	1 (0.2)	0	0	0	1 (0.1)	0
Thrombosis	0	0	1 (0.2)	0	1 (0.1)	0

(Source:

Abbreviations in table: COPD, ; CIDP, ; DVT; INR,

*Group of 4 primary symptoms associated with naldemedine GI toxicity

**Multiple concurrent SAEs, presenting with hematochezia, hypotension, and mental status changes; cardiac ischemia identified during hospitalization- event adjudicated as MACE (MI, type 2) by the

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Hypersensitivity

There are 3 total subjects in the pooled phase 3 safety population with events of interest related to hypersensitivity (all in the naldemedine arm).

Two subjects with study discontinuation due to events consistent with hypersensitivity (Subject 10602-001 with an SAE meeting criteria for anaphylaxis [9] and Subject 52369-012). Both of these subjects experienced gastrointestinal symptoms characteristic of naldemedine GI toxicity.

- Subject 10602-002 (full narrative in Section 8.4.2): SAE of “allergic reaction” with onset of abdominal pain, diarrhea, vomiting, and bronchospasm within 2 hours of administration of the first dose of naldemedine. Based on Sampson criteria [9], this event meets criteria for possible anaphylaxis due to co-occurrence of respiratory distress and persistent gastrointestinal symptoms shortly after exposure to a potential allergen. The subject received treatment for this SAE in the emergency department, including antiemetics (promethazine, metoclopramide, and thiethylpromazine), inhaled beta 2-adrenergic agonist (fenoterol), omeprazole, and ambroxol (mucolytic). The subject recovered from the event on the same day. Study treatment was discontinued on Day 1 due to this event.

(Although this event meets diagnostic criteria for possible anaphylaxis, this reviewer notes that treatment of the event did not include antihistamines or corticosteroids. In addition, the subject did not experience hypotension or any cutaneous manifestations of hypersensitivity. On the contrary, the subject’s blood pressures were elevated during the event.)

- Subject 52369-012: AEs of abdominal pain/cramps, diarrhea, and rash on chest with onset within a couple of hours of the first dose of naldemedine. The subject discontinued study participation on Day 7 due to persistent symptoms. No treatment was administered for the AE.

(This event may represent a hypersensitivity reaction but does not meet criteria for anaphylaxis.[9])

One additional subject had a TEAE of rash (onset Study Day 2), leading to study discontinuation. This event of rash without associated symptoms could be considered a possible hypersensitivity reaction based on temporal relationship to study treatment.

- Subject 52426-013: 47-year-old female with medical history of hypersensitivity and eczema who developed a rash (left armpit) starting on Study Day 2 and rash (right armpit, moderate severity) starting on Study Day 6. Study treatment was discontinued on Day 6. The first occurrence of rash (left armpit, moderate severity) resolved on Day 10, and the second occurrence of rash (left armpit) resolved on Day 20. No treatment was provided for the rash. No other AEs were reported for this subject.

8.4.4. Significant Adverse Events

Summary of Significant Adverse Events

Gastrointestinal drug toxicity, presenting most commonly with symptoms of abdominal pain, diarrhea, nausea, and/or vomiting, was the most frequent type of adverse reaction in naldemedine clinical trials (i.e., adverse events reasonably attributable to study drug treatment). In the judgment of this reviewer, GI adverse reactions are the most significant contributor to the overall safety profile of this drug due, in part, to the disproportionate number of study discontinuations and/or treatment interruptions attributed to these reactions. Nevertheless, serious GI reactions were uncommon, and symptoms typically resolved rapidly upon treatment discontinuation or resolved spontaneously in spite of ongoing treatment. None of the treatment-emergent GI events were considered reasonably likely to be due to study drug treatment were associated with life-threatening complications or long-term sequelae. [The reader is referred to the Subsection below, entitled “Gastrointestinal (GI) Drug Reactions/Toxicity” for a more detailed review of GI safety data.]

Opioid withdrawal represented the other major group of naldemedine adverse reactions, with events (including possible cases-see definitions). Similar to GI reactions, opioid withdrawal events were non-life threatening, but are considered notable for their contribution to study discontinuations. The rate of opioid withdrawal was low’ no change to recommendations regarding doses is needed.

Gastrointestinal (GI) Drug Reactions/Toxicity

The most common presenting symptoms of naldemedine GI toxicity were abdominal pain, diarrhea, nausea, and vomiting. In controlled phase 3 studies, 20.9% of naldemedine-treated subjects experienced ≥ 1 of these 4 GI symptoms during study treatment (vs. of placebo-treated patients)—12-week studies and 52-week trial.

Abdominal pain and diarrhea

Although this is not a comprehensive list of AE terms corresponding to naldemedine ARs, and these symptoms also frequently with events not attributable to naldemedine treatment, this group of terms captures the majority of subjects who experienced naldemedine GI toxicity.

Though plausible and are described due to the risk of gastrointestinal perforation with PAMORA, for which cases have only been reported with subcutaneous Relistor but are considered a class-wide risk.

One distinguishing feature of GI toxicity is the generally early onset of symptoms, compared to

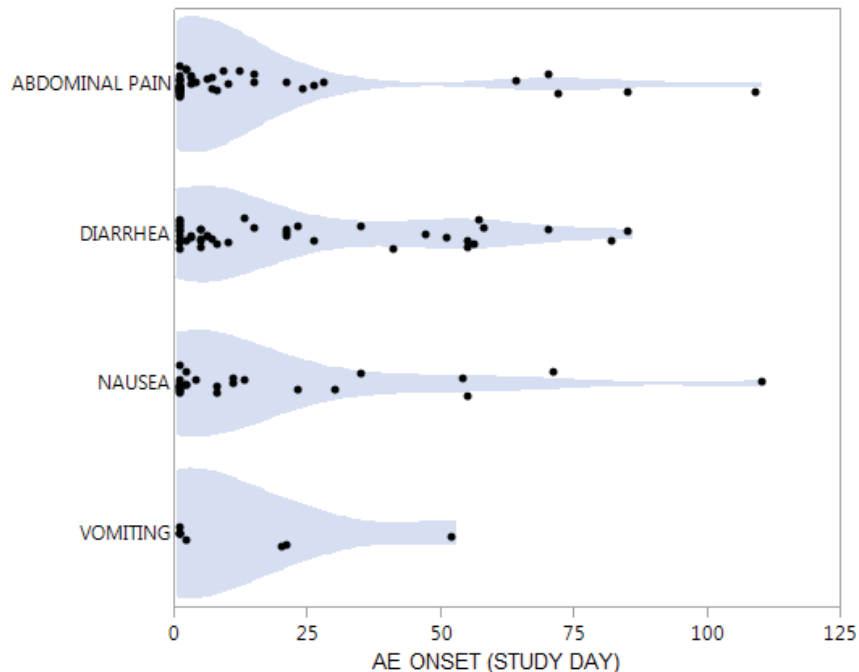
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GI events in the placebo arm which were more dispersed throughout study duration.

Of the naldemedine subjects who reported ≥ 1 GI AE, 51.5% reported onset of symptom(s) in the first week of treatment (29.7% on Study Day 1) during Week 1. By comparison, 26.1% of all subjects in the placebo arm with ≥ 1 GI AE had onset of symptoms during the first week of study treatment (5.9% on Day 1).

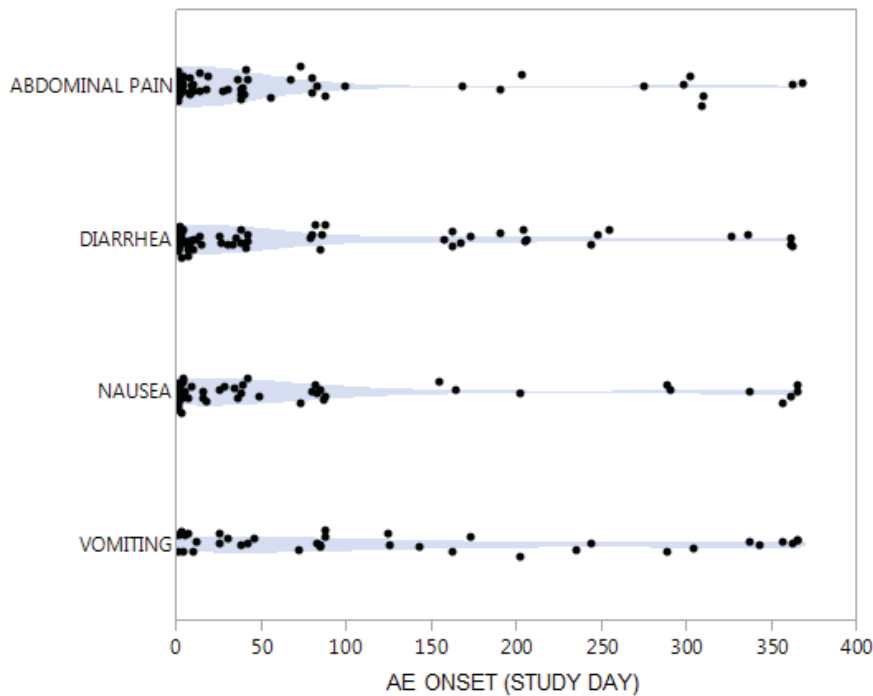
Figure 30 and Figure 31 show the distribution of AE onset for the GI AEs of abdominal pain, diarrhea, nausea, and vomiting for naldemedine-treated subjects in the 12-week trials (Studies V9231 and V9232) and Study V9235, respectively (subject's first episode only).

Figure 26: Onset (Study Day) of GI AEs in Naldemedine-Treated Subjects in Studies V9231 and V9232



(Source: Reviewer's figure)

Figure 27: Onset (Study Day) of GI AEs in Naldemedine-Treated Subjects in Study V9235

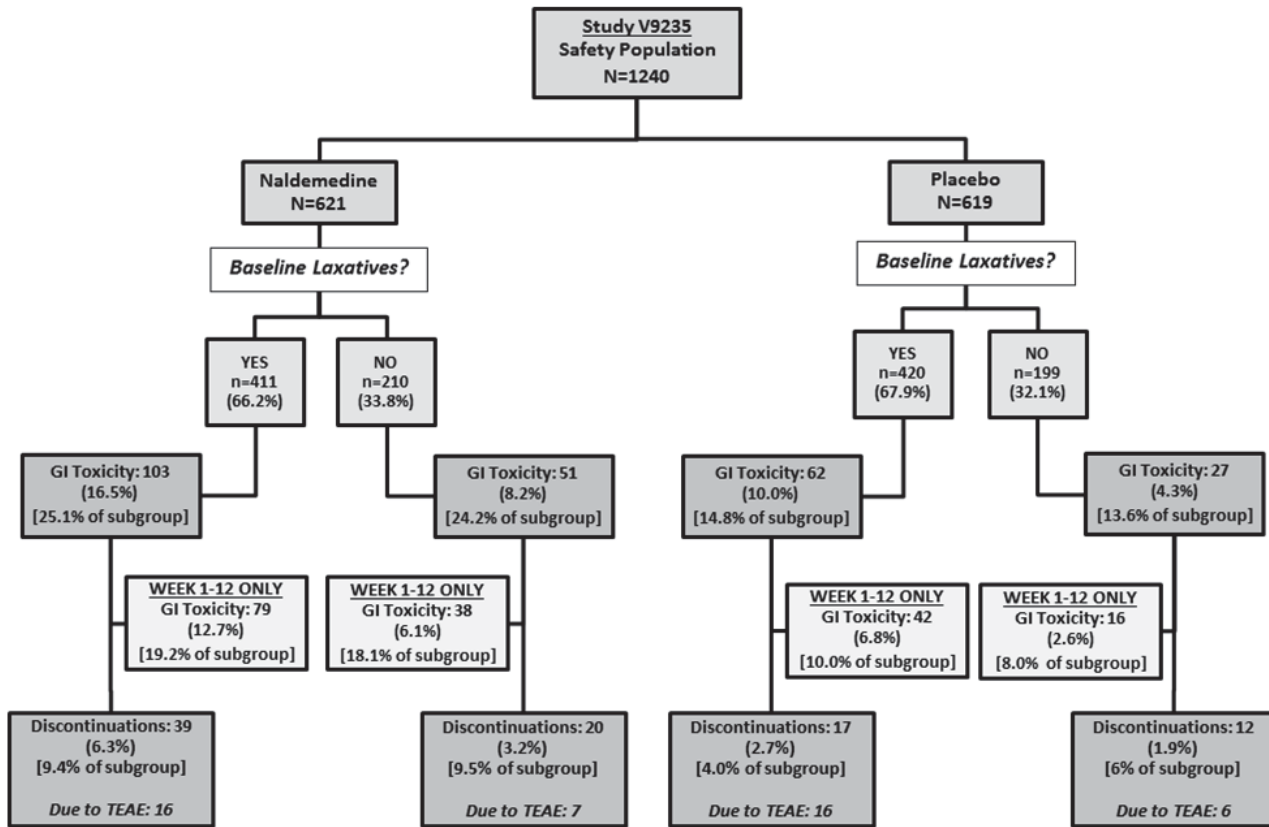


(Source: Reviewer's figure)

A major consideration during this review was the evaluation of naldemedine safety with concurrent laxative use. It is important to consider that ~2/3 of the V9235 study population was on a stable, established laxative at baseline that was continued into the treatment period when interpreting the relative frequencies of GI events.

A higher incidence of GI AEs was observed in the first 12 weeks of Study V9235, compared to Studies V9231 and V9232. However, it is difficult to attribute the higher rate of events to concomitant use of laxatives. In naldemedine-treated subject, the proportions of subjects with GI events and study discontinuations due to AEs were similar between subjects with and without baseline laxative regimens. This most notable difference was a higher rate of GI events in placebo subjects on baseline laxatives, compared to those without baseline laxative use.

Figure 28: GI AEs by Baseline Laxative Use in Study V9235



(Source: Reviewer's figure)

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Table 74 and Table 75 show the most common TEAEs reported during a 12-week treatment period in placebo-controlled phase 3 clinical trials. Events which occurred at a higher rate in naldemedine-treated subjects are shown in Table 74, while other TEAEs with incidence of $\geq 0.5\%$ for either a study arm, study population, or the entire pooled population, but occurring in naldemedine subjects at a similar or lower rate than placebo are shown in Table 75.

Data for the 2 replicate trials (Studies V9231 and V9232) have been pooled and are shown in comparison with data from Weeks 1 through 12 of Study V9235. Data for all 3 studies has not been pooled due to important differences in study design that impact the interpretation of safety data. Specifically, Study V9235 permitted concomitant maintenance laxative use during study participation, unlike Studies V9231 and V9232, in which patients were required to discontinue laxatives prior to study enrollment and permitted only specified rescue use of bisacodyl during the study treatment period. These V9235 safety data provide the basis for the Applicant's claim that naldemedine may be safely administered with or without laxatives without the need for medication adjustment prior to treatment initiation and therefore, require

separate evaluation from the other clinical trial safety data.

For AE tabulations, closely related dictionary-derived terms were combined under a single AE term. (A list is provided in the Appendix). For this application, TEAEs included events with onset during study treatment, i.e., the period from administration of the first dose through the last day of study treatment. Because the half-life of naldemedine is relatively short and delayed effects of the drug are unlikely, events with onset during the follow-up period were not included.

Subjects with multiple episodes of the same AE were counted only once per AE term, even if events were coded to >1 related dictionary-derived term. The identification of ARs (i.e., TEAEs reasonably likely to be caused by treatment with the study drug) was based on comparisons with placebo data, the relationship between AE onset and the timing of study treatment, and biological plausibility for a mechanism.

Table 75: Treatment-Emergent Adverse Events with Higher Incidence in the Naldemedine Arm and Occurring in ≥0.5% of Naldemedine-Treated Subjects (Either Pooled Population or Study Arm)

AE Term*	12-Week Studies (V9231 & V9232)		Study V9235: Weeks 1-12		Overall (12-Week Treatment)	
	Naldemedine (N=542)	Placebo (N=546)	Naldemedine (N=621)	Placebo (N=619)	Naldemedine (N=1163)	Placebo (N=1165)
Abdominal Pain*	42 (7.7)	11 (2.0)	67 (10.8)	28 (4.5)	109 (9.4)	39 (3.3)
Diarrhea	42 (7.7)	9 (1.6)	46 (7.4)	17 (2.7)	88 (7.6)	26 (2.2)
Nausea	23 (4.2)	13 (2.4)	35 (5.6)	23 (3.7)	58 (5.0)	36 (3.1)
Gastroenteritis*	13 (2.4)	7 (1.3)	17 (2.7)	7 (1.1)	40 (3.4)	14 (1.2)
Vomiting	8 (1.5)	5 (0.9)	17 (2.7)	10 (1.6)	35 (3.0)	15 (1.3)
Hyperhidrosis	8 (1.5)	3 (0.5)	9 (1.4)	5 (0.8)	17 (1.5)	8 (0.6)
Opiate withdrawal	2 (0.4)	1 (0.2)	10 (1.9)	5 (0.8)	12 (1.0)	6 (0.5)
Fatigue/Malaise	6 (1.1)	0	7 (1.3)	3 (0.5)	13 (1.1)	3 (0.3)
Flushing	4 (0.7)	3 (0.5)	7 (0.6)	3 (0.5)	11 (0.9)	6 (0.5)
Pyrexia	8 (1.5)	1 (0.2)	3 (0.5)	2 (0.3)	11 (0.9)	3 (0.3)
Hypertension*	7 (1.3)	1 (0.2)	3 (0.5)	3 (0.5)	10 (0.9)	4 (0.3)
Chills/cold sweats	4 (0.7)	1 (0.2)	4 (0.6)	3 (0.5)	8 (0.7)	4 (0.3)
Neck pain	4 (0.7)	1 (0.2)	6 (1.0)	0	10 (0.9)	1 (0.1)
Lacrimation increased	4 (0.7)	0	3 (0.5)	0	7 (0.6)	0
Oropharyngeal pain	5 (0.9)	0	2 (0.3)	4 (0.6)	7 (0.6)	4 (0.3)
Otitis	1 (0.2)	0	5 (0.8)	3 (0.5)	6 (0.5)	3 (0.3)
Weakness	1 (0.2)	0	4 (0.6)	1 (0.2)	5 (0.4)	1 (0.1)
Hyperphagia/ Appetite increased	1 (0.2)	0	4 (0.6)	0	5 (0.4)	0

(Source: Reviewer's table)

Table 76: Treatment-Emergent Adverse Events With Similar or Lower Incidence in the Naldemedine Arm and Occurring in ≥1% of Subjects in the Pooled Phase 3 Safety Population (or Single Arm)
(Bolded text represents events with notably higher incidence in the placebo population)

AE Term*	12-Week Studies (V9231 & V9232)		Study V9235 Weeks 1-12		Overall (12-Week Treatment)	
	Naldemedine (N=542)	Placebo (N=546)	Naldemedine (N=621)	Placebo (N=619)	Naldemedine (N=1163)	Placebo (N=1165)
Abdominal Distension	9 (1.6)	10 (1.8)	11 (1.8)	9 (1.5)	20 (1.7)	21 (1.8)
Anxiety	4 (0.7)	5 (0.9)	6 (1.0)	7 (1.1)	10 (0.9)	13 (1.1)
Arthralgia	6 (1.1)	5 (0.9)	10 (1.6)	9 (1.5)	16 (1.4)	14 (1.2)
Back Pain*	13 (2.4)	14 (2.6)	17 (2.7)	15 (2.4)	30 (2.6)	29 (2.5)
Bacteriuria	1 (0.2)	6 (1.1)	0	0	1 (0.1)	6 (0.5)
Bone fracture	4 (0.7)	1 (0.2)	2 (0.3)	10 (1.6)	6 (0.5)	11 (1.0)
Bronchitis*	6 (1.1)	5 (0.9)	7 (1.1)	5 (0.8)	13 (1.1)	10 (0.9)
Cellulitis	1 (0.2)	2 (0.4)	6 (1.0)	4 (0.6)	7 (0.6)	6 (0.5)
COPD*	3 (0.6)	3 (0.7)	4 (0.6)	6 (1.0)	7 (0.6)	9 (0.8)
Depression	1 (0.2)	2 (0.4)	5 (0.8)	4 (0.6)	6 (0.5)	6 (0.5)
Dizziness/Presyncope	4 (0.7)	3 (0.5)	7 (1.1)	6 (1.0)	11 (0.9)	9 (0.8)
Dyspepsia/GERD	2 (0.4)	4 (0.7)	5 (0.8)	8 (1.3)	7 (0.6)	12 (1.0)
Edema	5 (0.9)	2 (0.4)	4 (0.6)	6 (1.0)	9 (0.8)	8 (0.7)
Elevated CPK	4 (0.7)	7 (1.3)	1 (0.2)	0	5 (0.4)	7 (0.6)
Fall	2 (0.4)	6 (1.1)	3 (0.4)	4 (0.6)	5 (0.4)	10 (0.9)
Flatulence	9 (1.6)	13(2.4)	9 (1.4)	16 (2.6)	18 (1.5)	29 (2.5)
Flu/Influenza	5 (0.9)	3 (0.5)	7 (1.1)	7 (1.1)	12 (1.0)	10 (0.9)
Headache	15 (2.8)	10 (1.8)	19 (3.1)	22 (3.6)	34 (2.9)	32 (2.7)
Hematuria (all)*	5 (0.9)	7 (1.3)	2 (0.3)	0	7 (0.6)	7 (0.6)
Muscle spasms/twitching	4 (0.7)	4 (0.7)	5 (0.8)	6 (1.0)	9 (0.8)	10 (0.9)
Musculoskeletal pain*	5 (0.9)	3 (0.5)	7 (1.1)	7 (1.1)	12 (1.0)	10 (0.9)
Myalgia	6 (1.1)	12 (2.2)	10 (1.6)	10 (1.6)	16 (1.4)	22 (1.9)
Nasopharyngitis/URI	23 (4.2)	24 (4.4)	29 (4.7)	29 (4.7)	52 (4.5)	53 (4.5)
Pain in extremity	3 (0.6)	3 (0.6)	6 (1.0)	9 (1.5)	9 (0.8)	12 (1.0)
Pneumonia (all)*	0	2 (0.4)	6 (1.0)	7 (1.1)	6 (0.5)	9 (0.8)
Sinusitis*	6 (1.1)	12 (2.2)	10 (1.6)	10 (1.6)	16 (1.4)	22 (1.9)
Tooth infection/abscess	4 (0.7)	4 (0.7)	6 (1.0)	7 (1.1)	10 (0.9)	11 (0.9)
UTI (all)*	14 (2.6)	20 (3.7)	11 (1.8)	25 (4.0)	25 (2.1)	45 (3.9)

(Source: Reviewer's table)

By far, gastrointestinal (GI) symptoms comprise the largest group of treatment emergent adverse events (TEAEs). As shown in Table 75 and Table 76, GI AEs were common among both naldemedine- and placebo-treated patients, which can be attributed to the numerous confounding risk factors in this patient population, including the underlying condition of OIC, other opioid-related GI adverse effects, laxative use, (particularly stimulant laxatives such as bisacodyl), and side effects of other concomitant medications (e.g., NSAIDs, corticosteroids).

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Therefore, GI-related ARs (i.e., TEAEs reasonably likely to be due to study treatment) represent only one subset of GI-related AEs. As a result, the main challenge of this safety review was to adequately characterize these drug-related GI reactions, underscoring the critical importance of placebo-controlled safety data.

As shown in Table 75, the group of AEs identified that best represent the symptoms of GI toxicity associated with naldemedine treatment were particularly abdominal pain, diarrhea, nausea, and vomiting. A detailed discussion of naldemedine GI toxicity is provided in the previous section (Section 8.4.4). A group of 4 terms (abdominal pain, diarrhea, nausea, and vomiting), although not exceedingly specific for drug toxicity, appear to capture the majority of cases of naldemedine GI toxicity. Each of these symptoms occurred at higher rates among naldemedine-treated patients (vs. other common GI events, such as abdominal bloating and GERD, that are less likely to be associated with naldemedine treatment).

These GI symptoms can be distinguished from those in Table 76 which were not reported more frequently with naldemedine, and in some cases, such as GERD and flatulence, incidence was lower in the naldemedine group, and are more likely to be due to OIC or other opioid-mediated GI dysfunction.

Hypersensitivity: Two naldemedine-treated subjects with hypersensitivity events [Subjects 10602-002 (SAE) and 52369-012] leading to study discontinuation are discussed in Section 8.4.3. Serious hypersensitivity events have also been reported with other drugs in the PAMORA class and are described in the PI.

The AE dataset was searched for other possible hypersensitivity events using AE term including rash, urticaria, flushing, hypotension, lip/tongue swelling, and pruritus. All events with these terms were evaluated for co-occurrence with other hypersensitivity-related terms, timing of event onset, symptom duration, and resolution/persistence of symptoms with respect to study treatment. Gastrointestinal events were also evaluated for co-occurrence with these symptoms.

One additional subject was identified who experienced symptoms suggestive of hypersensitivity (10602-001), occurring in a naldemedine-treated subject who completed the entire 12-week period of Study V9231. No additional cases of possible anaphylaxis were identified.

- Subject 10602-001: Beginning on study day 1, the subject experienced onset nausea 1 hour after each dose of naldemedine, lasting for 2 hours. On Study Day 5, the subject also began experiencing mouth itching and nasal discharge 1 hour after each dose, also lasting for 2 hours. These symptoms persisted until the end of the 12-week study period. Symptoms were mild and did not lead to discontinuation. The subject did not receive treatment for these symptoms; however the reviewer notes that the subject was on daily antihistamine treatment with levocetirizine (prior and concomitant medication).

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(While these symptoms are consistent with a possible hypersensitivity reaction based on the nature and timing of symptoms, these AEs were mild and did not worsen over the 12-week treatment period despite ongoing treatment.)

Only 1 AE of isolated rash (i.e., no other concomitant symptoms) was identified which may represent a hypersensitivity reaction due to naldemedine. A relationship to study treatment was excluded for other AEs of rash, including urticaria, based on the timing of AE onset and resolution for those events.

- Subject 52426-013: 47-year-old female with medical history of hypersensitivity and eczema who developed a rash (left armpit) on Study Day 2 and rash (right armpit) on Study Day 6. Study treatment was discontinued on Day 6. The first occurrence of rash resolved on Day 10, and the second occurrence of rash resolved on Day 20. No treatment was provided for the rash.

8.4.6. Laboratory Findings

Summary of Laboratory Findings

Liver Events

In nonclinical studies, the liver was the primary target organ of toxicity, though abnormalities were only observed with highly suprathreshold doses. In the three Phase 3 studies (V9231, V9232, and V9235), pre-specified criteria were used to define “liver events”, which were reported using a specific Liver Event Form directly to the Investigator. The

- AST or ALT >5 times (x) the upper limit of normal (ULN)
- AST or ALT >3x the ULN and total bilirubin >2xULN or prothrombin time INR >1.5, if INR measured.
- AST or ALT >3xULN with signs or symptoms compatible with hepatitis or hypersensitivity (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia [>5%])
- AST or ALT >5xULN and the subject cannot be followed up weekly

Summary of Liver Events: In the phase 3, placebo-controlled safety population, 18 patients (9 patients in each treatment arm) were identified by the Applicant as having significant liver enzyme abnormalities. Of the naldemedine cases, this reviewer identified 2 cases which did not meet criteria for a liver event based on review of all laboratory and clinical data. No cases in either group met criteria for Hy’s law.

For 3 cases in the naldemedine group, an alternate explanation for the subject’s laboratory abnormalities could not be identified and were considered by this reviewer to be possibly

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attributable to study treatment. However, one of these patients had transaminase fluctuations following withdrawal of treatment that did not appear consistent with drug-induced liver injury (DILI). By comparison, an explanation for transaminase abnormalities in 5 of the 9 cases in the placebo group could not be determined.

Narratives and reviewer comments are provided for the 18 cases identified as liver events by the Applicant.

Naldemedine (n=9)

Subject ID	Age(yrs)/ Sex	Baseline Labs	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
11103-004	49/M	ALT/AST normal GGT 114(H)	85	ALT/AST >5xULN	Completed	Resolved	Likely related to celecoxib treatment

Subject's medical history is notable for ankylosing spondylitis and myofascial pain syndrome. At baseline, transaminases were normal, but GGT was elevated (114 U/L, ~2 times the ULN). At the time of randomization, the subject was taking etoricoxib. Due to a moderate increase in blood pressure, on Day 57 treatment with etoricoxib was discontinued celecoxib was started on Day 58. Celecoxib was discontinued on Day 84. At the last study visit on Day 85, the subject was found to have elevated transaminases >5 times the ULN (ALT 284 U/L, AST 150 U/L) and 2.3-fold increase in GGT from baseline (265 U/L). On Day 95 (unscheduled visit), labs were improving. On Day 113, ALT and AST values were normal (23 U/L, 20 U/L, respectively) and GGT values had returned to baseline (107 U/L).

No additional laboratory tests or procedures were performed as a result of the event. The principal investigator assessed the event as moderate in severity and not related to study drug.

Reviewer comment: This reviewer considers this event more likely due to celecoxib (known drug effect, timing of AE onset and new drug) than study treatment but cannot exclude the possibility of study drug reaction because both treatments were discontinued concurrently (end of study). The subject's baseline elevated GGT was noted.

Subject ID	Age(yrs)/ Sex	Baseline Labs	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
22312-009	54/M	ALT/AST normal GGT 270 (H)	33	ALT> 5x ULN	Withdrawn (AE)	Improved but not resolved	Possibly due to study drug

The subject was noted to have elevated ALT and AST on day 33 (1.8 and 1.6 times the ULN, respectively) with increased GGT to 603 U/L (>10 times the ULN), a 2.2-fold increase from baseline. Similar results were obtained at Day 55. The study drug was discontinued on day 63. Subsequent values on day 76 were higher with ALT>5 times the ULN (255 U/L) and AST 2 times the ULN. GGT was ~20 times the ULN, equivalent to a 3.7-fold increase from patient's baseline

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(see table below provided by Applicant). The subject was referred to a gastroenterologist for consultation; abdominal ultrasound done on Day 84 was normal. Serum transaminases on Day 81, 83, 90, 92, and 104 ranged from 100 to 157 U/L. Though lower than day 76 values (peak), there were fluctuations in transaminase levels, rather than a steady improvement (see table below provided by the applicant). The narrative provided by the applicant states that “on Day 140, results had returned to baseline.” However, slight elevations in ALT (54 U/L, 1.3 times the ULN), ALP (131 U/L) persisted, and GGT was 1.5-fold above baseline level (8.7 times the ULN). The event was assessed as iatrogenic and possibly related to study drug.

Analyte (NR)	Screening	Day 1	Day 33	Day 55	Day 76	Day 81	Day 83	Day 87	Day 90	Day 92	Day 104	Day 140
ALT/SGPT (6-41 U/L)	35	38	72	78	255	157	127	154	121	100	139	54
AST/SGOT (9-34 U/L)	33	36	55	53	73	51	52	56	60	51	43	32
ALP (37-116 U/L)	75	87	124	123	197	176	160	165	143	146	141	131
GGT (11-52 U/L)	270	288	603	685	1003		825	759	660	595	495	456

Reviewer comment: In the absence of an alternate explanation, this reviewer agrees that the event may be related to study drug treatment. However, the fluctuations in transaminase levels following study drug discontinuation are unusual. A full evaluation for other etiologies (hepatitis, cholestasis) was not performed. The outcome for this patient remains unclear due to the persistent abnormalities at the time of last follow-up. The subject’s baseline elevated GGT was noted.

Subject ID	Age(yrs)/ Sex	Baseline	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
50702-003	56/F	Day 1 (pre-dose) AST normal ALT 44 (H) GGT 240 (H) ALP 246 (H)	43	AST >5 x ULN	Completed	Resolved by report	Unknown

Relevant medical history includes obesity, medical induced failure of kidneys, and myocardial infarction. At screening, the subject had elevated GGT (266 U/L, 7 times the ULN). Less pronounced elevations in AST and ALP (both 2 times the ULN) were also noted, as well as a mildly elevated ALT (1.4 times ULN). On repeat testing during screening and pre-dose on day 1, AST levels were slightly above the ULN, and similar abnormalities for GGT and ALP were observed. At day 43, slight elevations in ALT and AST levels from baseline were noted, with more pronounced elevations on Day 85 (AST >5 times the ULN, ALT 2.8 times ULN). On Day 85, GGT increased 30% from baseline to 8.4 times the ULN. No additional evaluation was performed, and treatment remained unchanged. Per the Investigator, the liver enzymes were

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measured on Day 261 with normal results (values not available). The event was considered resolved. The Investigator assessed the event as moderate in severity and not related to study drug.

Analyte (NR)	Screening	Retest	Day 1	Day43	Day 85
ALT/SGPT (6 - 41U/L)	59	33	34	52	113
AST/SGOT (9 - 34U/L)	70	43	44	53	191
ALP (37 - 116U/L)	232	190	246	215	234
GGT (7 - 38U/L)	266	196	240	245	321

Clinical Reviewer comment: Based on the presence of baseline abnormalities, this reviewer agrees that a causal relationship between the event and study treatment cannot be established. The subject's baseline GGT >5 times the ULN is noted.

Subject ID	Age(yrs)/ Sex	Baseline	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
52225-006	46/F	Normal	244	ALT >5x ULN	Withdrawn	Resolving	Biliary obstruction

Medical history is notable for obesity, chronic fatigue syndrome, fibromyalgia, hypermobility joint syndrome, leg edema, and urinary tract infection. Screening and Day 1 pre-dose studies were normal. The patient's liver event (ALT>5 times the ULN) was noted on Day 244. However, abnormal ALP and GGT levels were first noted on Day 85 [ALP 153 U/L (1.4 times the ULN) and GGT 374 U/L (7 times the ULN)]. On Day 118, ALP and GGT levels were markedly improved and returned to normal on Day 176. Transaminase levels remained normal during this time. On Day 244, the patient had an elevated ALT of 289 U/L (7 times the ULN), along with an elevated ALP of 178 U/L (1.7 times the ULN). On Day 247, resonance cholangiopancreatography identified at least 1 calculus in the common bile duct. The study drug was discontinued due to the SAE of bile duct stone. The Investigator assessed the event as not related to study drug.

Reviewer comment: This patient's liver abnormalities can be attributed to cholelithiasis with biliary obstruction. Drug-induced hepatocellular liver injury due to naldemedine is considered unlikely in this patient. This patient has several known risk factors for cholelithiasis (female sex, age >40 years, obesity, and obesity; therefore, the SAE of bile duct stone does not represent an unexpected event. Although the liver was the target organ of toxicity at supratherapeutic doses in nonclinical trials, histopathological changes of hepatocellular injury were noted and were not consistent with cholestatic liver injury. This reviewer agrees that a causal relationship between this event and the study drug cannot be established.

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Subject ID	Age(yrs)/Sex	Baseline	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
52314-001	40/F	Normal	50	Did not meet criteria for liver event	Withdrawn (violation)	Ongoing	Suspected effect of gastric bypass surgery

On Day 50, the subject had elevated ALT (3 times the ULN) and AST (2.6 times the ULN). Past medical history was notable for morbid obesity, type 1 diabetes with diabetic neuropathy, prior cholecystectomy and gastric bypass surgery. The subject was withdrawn from the study on Day 49 due to protocol violation as the subject had a gastric bypass for obesity, which was an exclusion criterion. On Day 80, subsequent transaminases were 3 times the ULN (see table). The event was ongoing at last follow-up; last available ALT and AST values (day 91, 42 days after study drug discontinuation) were still >2 times the ULN. The bariatric surgeon and primary care physician were not concerned with the elevated AST and ALT levels and stated that this was a normal consequence of the procedure. The Investigator assessed the event as not related to study drug.

Reviewer comment: Based on the available information, this patient's laboratory abnormalities do not meet any of the criteria for a liver event. Although a reaction to study treatment cannot be excluded, this reviewer agrees that the patient's transaminase elevations were not likely due to study treatment.

Analyte (NR)	Screening	Day 1	Day 50	Day 80	Day 91
ALT/SGPT (6-41 U/L)	13	11	123	126	110
AST/SGOT (9-34 U/L)	20	15	90	102	88
ALP (37 - 116 U/L)	79	89	89	95	81
GGT (7 - 38 U/L)	8	8	11	18	19

Subject ID	Age(yrs)/Sex	Baseline	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
52319-008	56/F	Day 1 Pre-dose ALT 71 (H) AST 52 (H) GGT 72 (H)	365	AST > 5x ULN	Completed	Resolved	Probable fluctuation of pre-existing condition

Medical history notable for morbid obesity (BMI=51.3 kg/m²) fatty infiltration of the liver, elevated transaminases, chronic obstructive pulmonary disease, diabetes mellitus Type 2, fibromyalgia, gout, mixed hyperlipidemia, hypertension, rheumatoid arthritis, and sleep apnea. Screening and pre-dose (Day 1) ALT, AST, and GGT were abnormal (all 1 to 2 times the ULN). At the scheduled End-of-Treatment Visit (Day 365), increases in transaminase levels above baseline were noted (~2-fold and ~3-fold higher than baseline for ALT and AST, respectively). These abnormalities were flagged as a liver event due to AST level of 192 U/L (>5 times the ULN);

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see table below provided by the Applicant). At this visit, the subject reported nausea after taking routine medications on an empty stomach. On Day 368, AST had improved but ALT remained ~2-fold above baseline (125 U/L, 3 times the ULN). Both ALT and AST levels returned to baseline on Day 379, and the event was considered resolved. Of note, GGT level decreased to normal on Day 253 and subsequently remained below baseline. No additional evaluation was performed for the event. The Investigator assessed the TEAE of AST increased as moderate in severity and not related to study drug.

Analyte (NR)	Screening	Day 1	Day 43	Day 87	Day 169	Day 253	Day 339	Day 365	Day 368	Day 374	Day 379
ALT/SGPT (6 - 41 U/L)	50	71	92	82	57	36	83	119	125	101	56
AST/SGOT (9 - 34 U/L)	42	52	72	84	67	20	82	192	139	94	53
ALP (37 - 116 U/L)	70	65	90	76	94	96	93	103	84	84	90
GGT (7 - 38 U/L)	78	72	56	62	74	38	49	40	35	28	27

Reviewer's comment: This patient had a known diagnosis of fatty liver disease with associated transaminase elevations, and fluctuations in ALT/AST levels are common in this condition. Although the AST level was >5 times the ULN, the level was only modestly increased from baseline. This reviewer notes the patient's baseline elevated GGT, but also notes the improvement in GGT during study participation. This reviewer agrees that a causal relationship between this event and study drug treatment cannot be established.

Subject ID	Age(yrs) Sex	Baseline	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
52325-016	63/F	Normal	253	ALT/AST > 5x ULN	Withdrawn (SAE)	Resolved	Likely due to verapamil

Subject's medical history is notable for obesity, cholecystitis, prior cholecystectomy, cigarette smoking, melanoma (removed), hyperlipidemia, hypothyroidism, unilateral lower extremity edema, and sacroiliitis. Prior to this event, prednisone and verapamil were initiated for an unknown indication (Day 232), and acetaminophen 1000 mg BID was initiated for headaches (Day 239). Subject also reported new/increased alcohol use of 1-2 drinks per day (unknown start date).

On Day 253, the subject was noted to have elevated transaminases (ALT 466 U/L and AST 444 U/L, both >10 times the ULN), as well as elevated GGT (189 U/L, >5 times the ULN). Mild elevation of AP was also noted.

The study drug was withdrawn due to this SAE. Last day of treatment was Day 255. Repeat studies were obtained per protocol and remained elevated (see table below provided by the

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Applicant). On Day 256, there were similar elevations in transaminases and greater elevations in GGT (356 U/L, 9 times the ULN) and AP (1.7 times the ULN). Between Days 260 and 273, abnormalities persisted. During this period, the highest ALT level was on Day 260 (723 U/L), then ranged from 401 to 470 U/L. GGT levels increased persistently with maximum reported value of 820 U/L on Day 273 (18 days after the last dose of study drug). From Day 276 through Day 209, laboratory values ALT levels were somewhat lower (range 251-341 U/L), but remained >5 times ULN. Evaluation for hepatitis B, hepatitis C, CMV, and EBV was negative. An ultrasound of the abdomen showed only a prominent common bile duct post-cholecystectomy without intrahepatic duct dilatation and no acute findings.

In addition to discontinuation of study drug, alcohol, and acetaminophen were also discontinued. On Day 324, the subject discontinued therapy with verapamil, after which ALT and AST levels improved dramatically to levels only slightly above the ULN, and AP normalized (GGT not tested). Based on this, the Investigator attributed the SAE of hepatitis to verapamil and not related to the study drug.

Laboratory Test	Normal Range	Screening	Study Day																
			1	8	61	85	169	253	256	256	260	263	266	270	273	276	303	309	345
Bilirubin (Total)	0.10 - 1.10 mg/dL	0.30	0.26	0.24	0.34	0.36	0.33	0.56	0.57	0.63	2.17	0.72	1.13	0.57	0.43	0.36	0.35	0.8	
ALT/SGPT	6 - 41 U/L	34	82	32	45	44	35	468	493	520	723	401	488	423	470	305	341	251	43
AST/SGOT	9 - 34 U/L	27	69	26	41	38	32	444	367	386	446	208	539	314	422	160	230	129	39
Alkaline Phosphatase	37 - 116 U/L	46	52	45	44	40	40	132	201	209	445	350	418	505	557	526	582	444	91
Gamma Glutamyl Transferase	7 - 38 U/L	25	33	21	16	19	19	189	356				733	820					

Reviewer comment: This reviewer agrees that the onset and resolution of this TEAE are consistent with reaction to verapamil. The lack of improvement following study drug discontinuation also indicates that this is event was not related to treatment with the study drug.

Subject ID	Age(yrs) Sex	Baseline	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
52333-020	62/F	ALT normal AST normal GGT 207 (H)	1	Did not meet criteria for liver event	Completed	Resolved	Likely due to viral infection

The subject's medical history was notable for cardiomegaly, diverticulosis, hiatal hernia in cardia, prior cholecystectomy, and scleroderma. Screening transaminase levels were normal transaminase levels, but Day 1 pre-dose ALT was 81 and AST was 135 (2 and 4 times the ULN, respectively). Pre-treatment GGT levels were abnormal (4 times ULN at screening; see table below provided by the Applicant). The subject reported symptoms of an upper respiratory infection on Day 2. Repeat transaminase levels were normal on Day 6. The GGT level was

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similar to baseline. Study treatment was interrupted on Day 4 and resumed on Day 9. The subject completed the study. The Investigator assessed the event as mild in severity and not related to study drug.

Analyte (NR)	Screening	Day 1	Day 6	Day 29	Day 43	Day 87	Day 169
ALT/SGPT (6 - 41 U/L)	25	81	32	32	20	28	22
AST/SGOT (9 - 34 U/L)	23	135	24	25	24	32	23
ALP (37 - 116 U/L)	89	120	93	95	79	84	78
GGT (11 - 52 U/L)	207	419	275	352	196	150	147

Reviewer comment: Laboratory abnormalities occurred prior to first naldemedine dose and resolved spontaneously without recurrence. This AE also does not clearly meet criteria for a liver event. This reviewer agrees that this event is not related to study drug. The subject's persistently elevated GGT level, including baseline was noted.

Subject ID	Age(yrs) Sex	Baseline	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
52387-015	47/F	ALT/AST normal GGT 107 (H)	84	ALT >5xULN	Withdrawn	Resolving	Possibly due to study drug

At baseline, the subject had an elevated GGT of 107 U/L (2.8 times the ULN). Serum transaminases were normal. On Day 84, the subject was noted to have an ALT level >5 times the ULN (224 U/L). Other liver enzymes were also abnormal—AST 147 U/L (4.3 times the ULN), GGT (4.7 times the ULN and 1.7-fold increase from baseline), and AP 151 U/L (1.3 times the ULN; see table below provided by the Applicant). The subject was withdrawn from the study due to this TEAE. Repeat transaminases were normal on Day 93, and these TEAEs were considered resolved, although AP was still slightly elevated on Day 121 with GGT level 1.5-fold higher than baseline. The Investigator assessed these TEAEs as severe in severity and possibly related to study drug.

Analyte (NR)	Screening	Day 1	Day 42	Day 84	Day 86	Day 93	Day 100	Day 121
ALT/SGPT (6 - 41 U/L)	20	15	35	224	153	47	37	31
AST/SGOT (9 - 34 U/L)	16	13	29	147	73	21	31	15
ALP (37 - 116 U/L)	107	96	115	151	163	133	130	132
GGT (7 - 38 U/L)	107	74	160	179	202	225	203	156

Reviewer comment: This reviewer agrees that with the investigator assessment that a causal association between this event and study drug treatment is possible. The baseline GGT elevation is noted. This reviewer notes that the outcome of this event is not fully known due to the AP and GGT elevations at last evaluation. Additional evaluation may have been warranted.

Placebo (n=9)

Subject ID	Age(yrs) Sex	Baseline	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
22314-013	62/F	ALT/AST normal GGT 72 (H)	68	ALT >5 x ULN	Interrupted/ Completed	Resolved	Concomitant medication

The subject's medical history was notable for obesity, hypertension, hypercholesterolemia, systemic lupus erythematosus, prior cholecystectomy, , fibromyalgia, recurrent UTIs, rheumatic fever, Raynaud's phenomenon, and history of typhoid fever. Baseline GGT level was elevated (72 U/L, 1.9 times the ULN). Transaminase levels were normal. At the time of randomization, the subject was taking prednisone, ibuprofen, and Excedrin Migraine. At an unscheduled visit on Day 68, the subject was found to have an ALT level >5 times the ULN (222 U/L), elevated AST (87 U/L, 2.6 times the ULN), and increased GGT level (247 U/L, 6.5 times the ULN and 3.4 fold increase from baseline). ALP level was also slightly elevated. Study treatment was interrupted due to the AE. A drug interaction was suspected, and treatment with prednisone, ibuprofen, and Excedrin Migraine were also discontinued. Transaminase levels returned to normal on Day 78; however, GGT remained ~2-fold higher than baseline (136 U/L). The subject restarted the study drug on her own on Day 80. GGT level was improved on day 87 and returned to baseline on Day 115. No additional laboratory tests or procedures were performed as a result of the event. The investigator assessed the elevated laboratory results as not clinically significant. No action was taken with study drug due to this event, and the subject completed the study. The investigator assessed the event as moderate in severity and possibly related to study drug.

Analyte (NR)	Screening	Day 1	Day 31	Day 57	Day 64	Day 68	Day 72	Day 78	Day 87	Day 115
ALT/SGPT (6-41U/L)	34	25	31	15	15	222	67	29	20	16
AST/SGOT (9-34U/L)	23	21	18	13	12	87	17	23	19	16
ALP (37-116U/L)	69	65	64	63	65	132	108	89	83	85
GGT (7-38U/L)	72	65	62	55	44	247	174	136	99	81

Reviewer comment: Although the investigator suspected a possible causal relationship of study drug interaction, other concomitant medications were also suspected of contributing to the subject's laboratory abnormalities. Because this patient was on placebo and improvements occurred with discontinuation of other possible offending agents, this event was likely caused by concomitant medication therapy. This placebo patient highlights the polypharmacy of many of the patients in this study population.

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Subject ID	Age(yrs) Sex	Baseline	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
22354-007	46/F	ALT/AST normal GGT 60 (H)	1	ALT >5 x ULN	Interrupted/ Completed	Resolved	Unknown

The subject's medical history was notable for melanoma, chronic low back pain, and asthma. At screening, GGT level was elevated (60 U/L, 1.6 times the ULN). On day 1 (pre-dose), ALT and AST were elevated (231 and 104 U/L, respectively). ALT level was >5 times the ULN. GGT level was also increased >2-fold above baseline (166 U/L). On Day 3, AST level was normal and ALT level was improved. Transaminase levels normalized by Day 9 and GGT returned to baseline on Day 18. Another elevation in ALT (124 U/L, 3 times the ULN), accompanied by an increase in GGT (124 U/L), occurred on Day 57. Repeat values were normal on Day 91. (Of note, this was the first GGT level in the normal range).

The study drug (placebo) was interrupted for 19 days and restarted on Day 21. Study treatment was not changed due to the Day 57 laboratory results. The subject completed the study. The investigator assessed the event as not related to study drug.

Analyte (NR)	Screening	Day 1	Day 3	Day 9	Day 18	Day 29	Day 57	Day 91
ALT/SGPT (6-41U/L)	22	231	69	24	12	13	121	11
AST/SGOT (9-34U/L)	15	104	14	10	13	12	20	12
ALP (37-116U/L)	96	115	98	106	93	85	94	98
GGT (7-38U/L)	60	166		87	55	50	124	37

Reviewer comment: The onset of this event preceded the first dose of study drug. The subject's baseline elevation in GGT is noted, as is the recrudescence in ALT in GGT on Day 57.

Subject ID	Age(yrs) Sex	Baseline	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
22359-019	58/F	ALT/AST normal GGT 60 (H)	25	ALT >5 x ULN	Withdrawn	Resolved	Acute illness

The subject's medical history is notable for obesity, hydrocephalus with ventricular shunt placement, headaches, chronic UTIs, urinary incontinence, absence seizures, hypothyroidism, sleep apnea, throat cancer, and gastric ulcer. At baseline, GGT level was elevated (60 U/L at screening and 166 U/L pre-dose on Day 1). Transaminase levels were normal. On Day 25, the subject was hospitalized for altered mental status and a fall. Other symptoms included hypertension, fever, hypoxia, and pneumonia. Hospital laboratory studies reportedly showed elevated transaminases (results not available). The study drug was discontinued during this SAE. On Day 56, serum transaminases returned to baseline (no GGT available). On Day 67, GGT level was lower than pre-dose level. The investigator assessed the event as severe and not related to study drug.

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Analyte (NR)	Screening	Day 1	Day 56	Day 67
ALT/SGPT (6-41U/L)	7	7	12	8
AST/SGOT (9-34U/L)	13	14	11	13
ALP (37-116U/L)	96	115	98	106
GGT (7-38U/L)	60	166		87

Reviewer comment: This patient's liver test abnormalities were likely due to the acute illness (SAE of pneumonia with altered mental status, hypoxia, and fall). This placebo patient underscores the high degree of morbidity in this study population.

Subject ID	Age(yrs) Sex	Baseline	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
50403-002	60/M	ALT/AST normal GGT 55 (H)	76	ALT/AST >5 x ULN	Interrupted/ completed	Resolved	Unknown

The subject's medical history is notable for coronary artery disease, dyslipidemia, hypertension, chronic obstructive pulmonary disease, lower extremity edema, and recurrent gastritis. At Screening and Day 1, transaminase levels were normal. GGT level was minimally elevated. On Day 76, ALT and AST levels were >5 times the ULN (353 and 377 U/L, respectively). On Day 78, transaminase levels were improved. AST level was normal by Day 81. On day 85, ALT was markedly improved and normalized by day 167. On this day, an elevated GGT of 86 U/L (1.7 times the ULN) was noted. Study treatment was interrupted on Day 77. The subject restarted the study drug on his own on Day 89 and completed the study. No laboratory tests or procedures were performed as a result of the event. On Day 245, the event was considered resolved. The Investigator assessed the non-serious TEAE of elevated liver enzymes as moderate in severity and possibly related to study drug.

Analyte (NR)	Screening	Day 1	Day 34	Day 76	Day 78	Day 81	Day 85	Day 167	Day 245	Day 328	Day 356	Day 370
ALT/SGPT (6 - 41 U/L)	39	41	41	353	169	80	58	38	31	32	32	24
AST/SGOT (9 - 34 U/L)	26	34	25	377	68	32	31	23	21	24	22	19
ALP (37 - 116 U/L)	71	62	60	60	62	62	54	94	57	62	63	57
GGT (11 - 52 U/L)	55	55	52	51	.	.	62	86	59	45	34	27

Reviewer comment: These liver test abnormalities (elevated transaminases with later rise in GGT, improvement upon discontinuation of treatment) follow the pattern of drug-induced liver injury (DILI), though not meeting criteria for Hy's Law. However, this would be considered a successful re-challenge (i.e., not DILI) in a patient receiving study treatment.

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Subject ID	Age(yrs) Sex	Baseline	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
52361-002	46/M	Normal	1	AST >5 x ULN	Withdrawn	Resolved	Likely high-dose acetaminophen

Baseline ALT, AST, ALP, and GGT were normal. On Day 335, ALT was 140 U/L (3.4 times the ULN) and AST was 241 U/L (>5 times the ULN). GGT and AP were normal (see the table below provided by the Applicant). The Investigator attributed the elevation of liver enzymes to high-dose acetaminophen (1 gram daily). Study treatment was discontinued (last dose on Day 336) due to this TEAE. On Day 339, AST was normal, and ALT was only mildly elevated. ALT normalized by Day 343. The Investigator assessed the TEAEs as severe in severity and not related to study drug.

Analyte (NR)	Screening	Day 1	Day 43	Day 83	Day 162	Day 188	Day 276	Day 335	Day 339	Day 343	Day 367	Day 381
ALT/SGPT (6 - 41 U/L)	18	15	12	16	14	14	21	140	55	27	13	15
AST/SGOT (9 - 34 U/L)	14	17	11	13	16	14	20	241	33	18	17	15
ALP (37 - 116 U/L)	74	77	62	69	70	67	73	58	54	59	56	52
GGT (11 - 52 U/L)	40	47	37	34	43	37	76	48		41	36	34

Reviewer comment: In this placebo patient, high-dose acetaminophen was likely the cause for the patient's transaminase abnormalities. However, the improvement occurred following both acetaminophen and study drug discontinuation (placebo), which would have made it difficult to exclude the possibility of a study treatment effect.

Subject ID	Age(yrs) Sex	Baseline	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
52460-002	30/F	Day 1 (pre-dose) ALT 164 AST 124 AP 170 GGT 106	1	ALT/AST >5 x ULN	Withdrawn	Ongoing	Hepatitis C

The subject's medical history was notable for obesity, COPD, polycystic ovarian syndrome, and seizures. At screening, minimal elevations were noted in AST, ALP, and GGT. On Day 1 (pre-dose), transaminase levels were ~4 times the ULN, and ALP and GGT were higher than screening levels(see table below provided by the Applicant). On Day 6, transaminase levels continued to increase (ALT 194 and AST 121) and remained elevated through Day 36, with AT levels fluctuating between 164 and 185 U/L). GGT levels rose steadily during this period, increasing

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from 123 to 182 U/L. At last evaluation (Day 43), transaminases were improved but still elevated (ALT 108 and AST 66), and GGT level was still >2.5-fold higher than baseline. The study drug was discontinued on Day 6. The subject reported dizziness, weakness, and an increase in tremors. It was discovered that the subject had contracted hepatitis C prior to randomization and start of study medication. The subject was withdrawn from the study. The investigator assessed the event as severe in severity and not related to study drug.

Analyte (NR)	Screening	Day 1	Day 6	Day 13	Day 19	Day 29	Day 29	Day 36	Day 43
ALT/SGPT (6 - 41 U/L)	41	164	194	164	167	185	184	165	108
AST/SGOT (9 - 34 U/L)	38	124	121	98	96	115	113	89	66
ALP (37 - 116 U/L)	127	170	195	180	190	191	191	182	162
GGT (11 - 52 U/L)	57	106	123	159	161	185		182	146

Reviewer comment: This event of abnormal liver enzymes in a placebo patient was due to Hepatitis C infection.

Subject ID	Age(yrs)/ Sex	Baseline	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
52457-005	42/F	Normal	172	ALT/AST >5 x ULN	Interrupted	Resolved	Unknown

The subject's medical history was notable for obesity, anemia, and type 2 diabetes mellitus. Baseline ALT, ALP, and GGT were normal. On Day 172, ALT was 209 U/L (>5 times the ULN), and AST was 137 (4 times the ULN). GGT was also elevated (<2 times the ULN; see table below provided by the Sponsor). Transaminase levels were markedly improved on Day 172 and normal on Day 180. The study medication was temporarily withheld from Day 175 to Day 188. The Subject later withdrew from the study (Day 263) due to scheduling conflicts. The Investigator assessed the TEAE as not related to study drug.

Analyte (NR)	Screening	Day 1	Day 46	Day 84	Day 172	Day 176	Day 180	Day 203
ALT/SGPT (6 - 41 U/L)	28	25	22	16	209	71	37	22
AST/SGOT (9 - 34 U/L)	35	33	25	22	137	35	30	27
ALP (37 - 116 U/L)	46	42	47	44	58	68	56	52
GGT (7 - 38 U/L)	12	14	16	12	65			

Reviewer comment: Although these liver test abnormalities occurred during study treatment (placebo), levels were already markedly improved prior to interrupting study treatment.

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Subject ID	Age(yrs)/ Sex	Baseline	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
52470-004	54/M	Normal	249	AST >5 x ULN	Withdrawn	Resolved	Unknown

Medical history was notable for schizophrenia. Baseline transaminases, AP, and GGT were normal. On Day 249, ALT was 65 U/L and AST was 211 U/L (>5 times the ULN). On Day 252, ALT rose to 125 U/L (>3 times the ULN), and AST increased to 272 U/L (8 times the ULN). GGT and AP remained normal (see table below provided by the Applicant). Improvement of transaminase levels was noted on Days 254 and 256, and levels were normal on Day 259. Study treatment was withdrawn due to this TEAE. Last dose of study drug was on Day 252. No additional evaluation was performed. On Day 254, the TEAEs were considered resolved. The Investigator assessed as the event not related to study drug.

Laboratory Test (Normal Range)	Screening	Day 1	Day 42	Day 85	Day 169	Day 249	Day 252	Day 254	Day 256	Day 259	Day 270	Day 298
ALT/SGPT (6-41 U/L)	13	16	15	12	19	65	125	86	60	35	16	12
AST/SGOT (9-34 U/L)	24	26	23	22	26	211	272	100	49	28	22	24
Alkaline Phosphatase (37-116 U/L)	63	62	72	60	73	72	74	75	77	72	76	65
GGT (7-38 U/L)	22	19	20	17	17	19	19	18	21	20	19	17

Reviewer comment: These liver test abnormalities occurred during study treatment (placebo) and improved upon study drug discontinuation. No additional evaluation was conducted to determine the etiology of these abnormalities. In the absence of an alternative explanation for these transaminase elevations, it is unclear why the investigator did not consider the event to be possibly due to study treatment.

Subject ID	Age(yrs) Sex	Baseline	AE Onset (day)	Event Type	Disposition	Outcome	Suspected Etiology
52470-006	55/M	Normal	343	AST >5 x ULN	Withdrawn	Resolved	Unknown

The subject's medical history is notable for diabetes mellitus type 2, hypercholesterolemia, and hypertension. At screening and on Day 1 (pre-dose), ALT was elevated (~2 times the ULN; see

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the table below provided by the Applicant). GGT was also minimally elevated at screening but normal on Day 1. ALT and GGT levels remained stable through Day 253. On Day 343, increased ALT above baseline (124 U/L, 3 times the ULN) and AST level >5 times the ULN were noted. At this time, GGT also was increased to 189 (~5 times the ULN). Levels remained elevated through Day 361 (see table), were improved on Day 372. At the last evaluation, the AST level had returned to normal and ALT level was similar to baseline, but GGT remained elevated (2-fold higher than baseline). The study drug was withdrawn due to this TEAE. The last dose of study drug was on Day 344. No additional evaluation was performed for these events.. The Investigator assessed the events as not related to study drug.

Laboratory Test (Normal Range)	Screening	Day 1	Day 46	Day 84	Day 95	Day 173	Day 253	Day 343	Day 347	Day 351	Day 354	Day 361	Day 372
ALT/SGPT (6-41 U/L)	85	84	90	82	91	95	95	124	114	132	117	106	98
AST/SGOT (9-34 U/L)	27	30	25	36	28	27	22	177	61	65	56	148	24
Alkaline Phosphatase (37-116 U/L)	85	84	90	82	91	95	95	124	114	132	117	106	98
GGT (7-38 U/L)	43	36	42	36	40	38	37	189	152	187	145	108	86

Reviewer comment: These onset of these liver test abnormalities occurred during study treatment (placebo). Levels fluctuated somewhat following study drug discontinuation, but were general improved upon study drug discontinuation. No additional evaluation was conducted to determine the etiology of these abnormalities. In the absence of an alternative explanation for these transaminase elevations, an association between the event and study drug treatment could not be excluded based on blinded assessment.

Renal Function

No changes in renal function were attributable to naldemedine treatment, with the exception of those secondary to pre-renal azotemia, in which GI toxicity may have resulted in hypovolemia in some cases and were reversible. For laboratory data (BUN and creatinine), no differences were noted between groups.

Serum Lipids

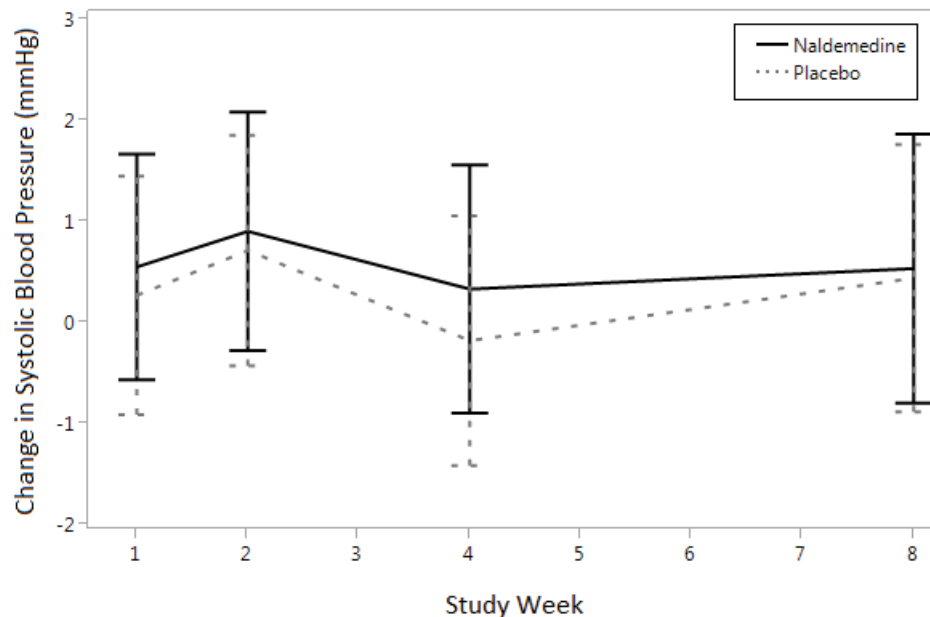
In AE data, treatment-emergent cases of hyperlipidemia (cholesterol and/or triglyceride) were reported more frequently in the naldemedine group. However, based on laboratory data from the pooled phase 3 safety population, naldemedine treatment was not associated with higher

cholesterol or triglyceride levels at any individual time point or greater mean change from baseline, regardless of subjects baseline levels or duration of treatment.

8.4.7. Vital Signs

Overall, mean changes in vital signs were small, and no differences between treatment groups could be identified. Because TEAE data (e.g., AEs of tachycardia, hypertension, etc.) suggested a possible effect of naldemedine on blood pressure and/or heart rate, analyses of vital sign data are presented below, demonstrating minimal changes from baseline observed in clinical trials. For pulse, systolic blood pressure, and diastolic blood pressure, mean changes were <3 beats/min or mmHg at all time points. Plots for each of these 3 parameters (pulse, systolic blood pressure, and diastolic blood pressure) are shown for the 12-week studies and the long-term study (V9235)—Figures 35-37 for Studies V9231 & V9232 and Figures 38-40 for Study V9235.

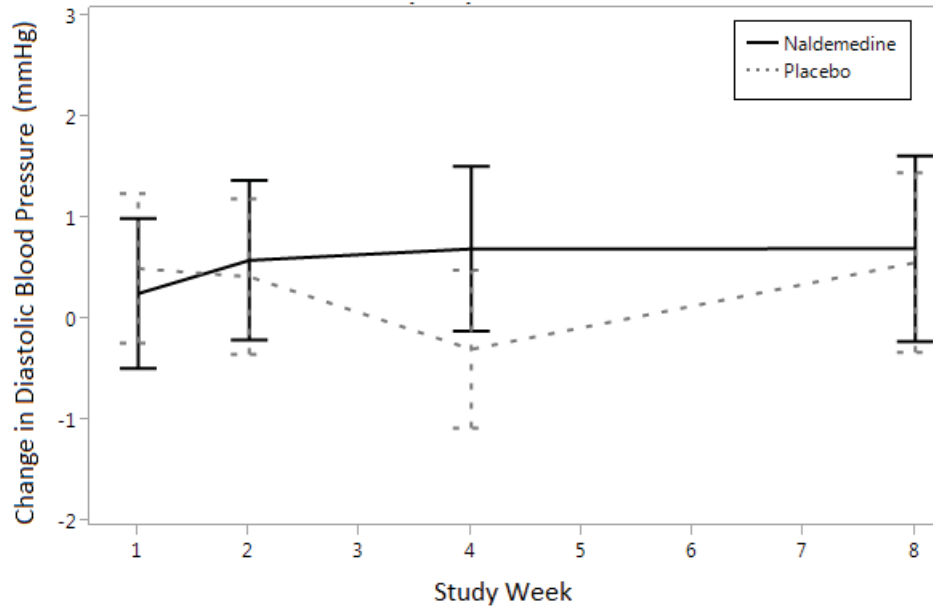
Figure 29: Change in Systolic Blood Pressure (mmHg) from Baseline in Studies V9231 & V9232, ITT Population (Mean $\pm$ 95% CI)



(Source: Reviewer's figure)

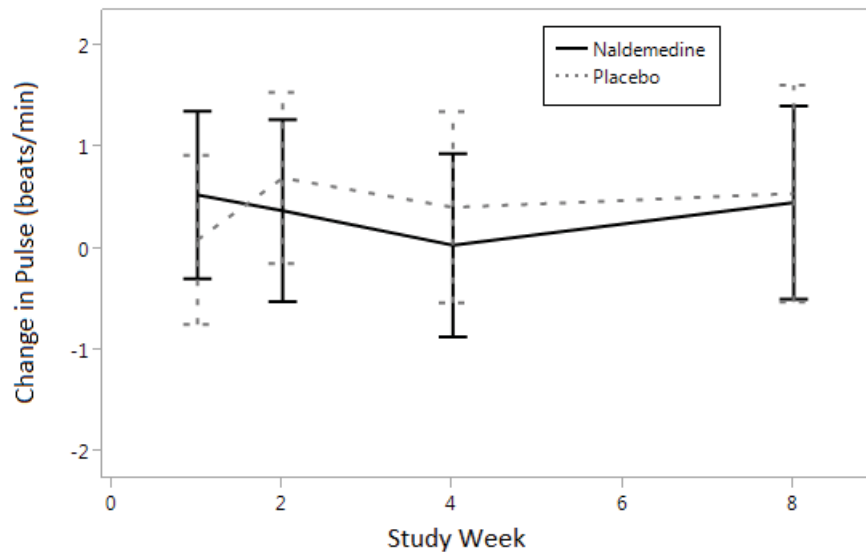
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Figure 30: Change in Diastolic Blood Pressure (mmHg) from Baseline in Studies V9231 & V9232, ITT Population (Mean $\pm$ 95% CI)



(Source: Reviewer's figure)

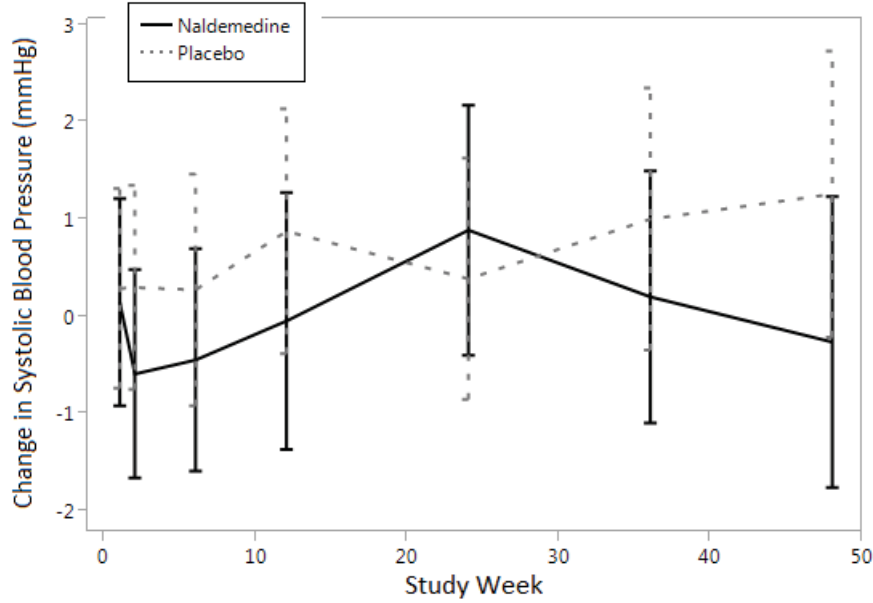
Figure 31: Change in Pulse Rate (Beats/Minute) from Baseline in Studies V9231 & V9232, ITT Population (Mean $\pm$ 95% CI)



(Source: Reviewer's figure)

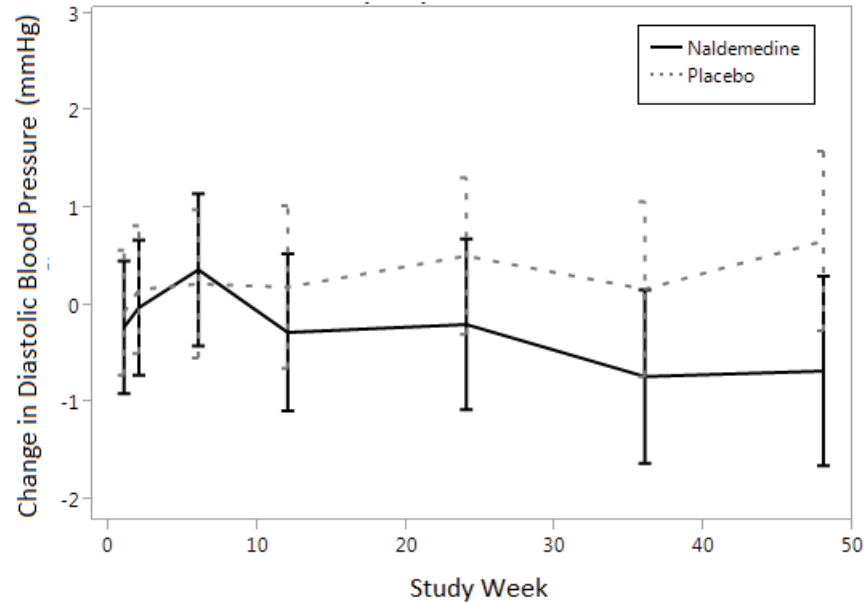
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Figure 32: Change in Systolic Blood Pressure (mmHg) from Baseline in Studies V9235, ITT Population (Mean $\pm$ 95% CI)



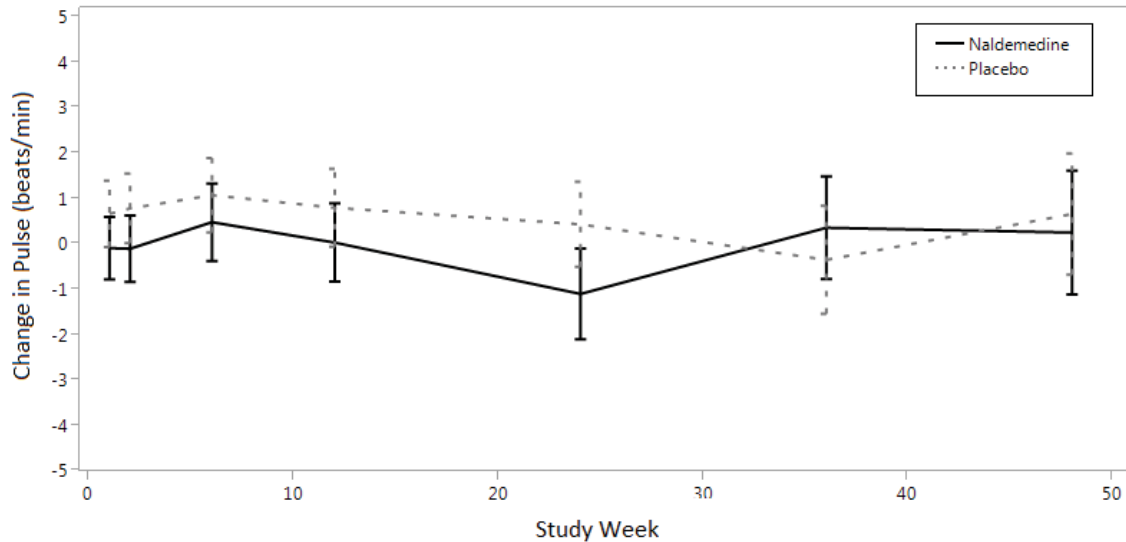
(Source: Reviewer's figure)

Figure 33: Change in Diastolic Blood Pressure (mmHg) from Baseline in Study V9235, ITT Population (Mean $\pm$ 95% CI)



(Source: Reviewer's figure)

Figure 34: Change in Pulse Rate (Beats/Minute) from Baseline in Study V9235, ITT Population (Mean $\pm$ 95% CI)



(Source: Reviewer's figure)

8.4.8. Electrocardiograms (ECGs)

Summary of ECG findings: Assessments of the arrhythmogenic potential of naldemedine included a phase 1 formal QTc study in healthy individuals (formally reviewed by the FDA QT Interdisciplinary Review Team. Electrocardiograms (ECG) were also included in the safety assessments of all clinical trials. Overall, no clinically meaningful safety findings or trends were noted in ECG assessments conducted in clinical trials.

8.4.9. QT

The Applicant conducted a Phase 1 PK/PD Study (Study 1204V9219) in 56 healthy individuals to evaluate the effect of naldemedine on the QT interval. Prior to initiation, the Applicant submitted the study protocol for Agency concurrence

Results: Prolonged QTc was reported in 1 subject. The QTc abnormality was mild and resolved without clinical intervention. This TEAE was considered not related to study drug by the investigator. Other abnormal ECG values were considered not clinically significant.

Overall, there were no deaths, SAEs, other significant AEs, or AEs leading to study discontinuation. No treatment-emergent vital sign abnormalities or physical examination findings were reported.

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8.4.10. Immunogenicity

Not applicable

8.5. Analysis of Submission-Specific Safety Issues

Based on the known safety profile of the PAMORA drug class, clinical experience with these drugs, and safety concerns identified from drug development programs of other members of the PAMORA drug class, this reviewer identified the following submission-specific safety issues:

- Opioid withdrawal
- Interference with opioid analgesia
- Major adverse cardiac events (MACE)

The PI for other members of the PAMORA drug class contains contraindications/warnings regarding hypersensitivity and gastrointestinal (GI) perforation. One serious hypersensitivity reaction leading to study discontinuation occurred in phase 3 trials (discussed in Sections 8.4.2 and 8.4.3). No events of GI perforation occurred in naldemedine clinical trials. However, the pathophysiology of PAMORA-associated GI perforation may be due to treatment-related intestinal blood flow. For this reason, special attention was given to TEAEs considered vascular in origin and are discussed throughout the safety review.

8.5.1. Opioid Withdrawal (OW)

In spite of the restricted passage of naldemedine and other PAMORAs, opioid withdrawal (OW) has been reported in association with these drugs and is included as a warning in the product labeling.

In naldemedine clinical trials, AEs were identified using 2 methods:

- prospective reporting and; these AEs were coded as OW (PT Drug withdrawal syndrome)
- retrospective chart review; this group of AEs was named "Possible OW"
- Possible opioid withdrawal was defined as at least three adverse reactions potentially related to opioid withdrawal (based on list of AE terms generated from opioid withdrawal scoring systems) that occurred on the same day and were not all related to the gastrointestinal system. (NOTE that the typical GI reactions with naldemedine (and other PAMORAs) are also among the most common symptoms of opiate withdrawal, possibly due to the similarity in mechanism (acute decrease in mu-opioid receptor-mediated effects).

Safety monitoring in the 3 controlled phase 3 naldemedine clinical trials also included scheduled OW assessments with 2 different patient-report questionnaires, the SOWS and

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COWS questionnaires.

A total of 49 subjects (34 subjects on naldemedine and 15 subjects on placebo) were identified as having ≥ 1 TEAE of OW (n=21) or possible OW (n=28). For patients with OW events, 13 were on naldemedine treatment vs. 8 on placebo (Table 77); and of the patients with possible OW, 21 were on naldemedine treatment vs. 7 on placebo. (Table 78) Only 2 subjects had more than 1 reported episode of opioid withdrawal. For 9 patients (4 with OW and 5 with possible OW), the DAAAP reviewer did not consider the event to meet the regulatory definition of an AR (i.e., an event for which there is sufficient basis to believe there is a causal relationship with the study drug) and are identified in Table 77 and Table 78.

In the phase 3 clinical trial safety population, there was a higher incidence of opioid withdrawal in naldemedine-treated subjects compared to placebo. In pooled Studies 1 and 2, the incidence of adverse reactions of opioid withdrawal was 1.5% (8/542) in the naldemedine arm and 0.5% (3/546) for placebo. In Study V9235, the incidence was 3.2% (20/621) in the naldemedine arm and 1.4% (9/619) in the placebo arm. (b) (4)

these subjects are included in the summary tables below). However, it should be noted, that even in cases with an identifiable cause, such as opioid noncompliance, naldemedine treatment could impact the onset and severity of withdrawal symptoms.

As shown in Table 77 and Table 78, discontinuation rates were similar between the OW and possible OW cases. For all patients, regardless of subject disposition, the OW or possible OW event resolved completely prior to the subject's last study visit.

In all cases of possible OW, subjects experienced GI symptoms. Because specific symptoms were not specified for many of the OW cases, it cannot be determined whether these cases were also universally associated with GI symptoms. In some cases of possible OW, GI symptoms were the only withdrawal symptoms identified. Therefore, it is unclear whether GI toxicity and isolated GI withdrawal symptoms represent distinct entities.

Because naldemedine is not supposed to be able to traverse the blood brain barrier (BBB), the occurrence of CNS symptoms of OW are concerning. Few subjects with conditions that affect the integrity of the BBB were enrolled in naldemedine clinical trials. However, none of these subjects were reported to have OW or identified as possible OW. An alternate explanation has been proposed, whereby a PAMORA may be able to "communicate" across the BBB without direct CNS penetration.[10] This is an important consideration related to both OW and possible effects on opioid analgesia.

These events were reviewed for concomitant use of CYP3A4/P-gp inhibitors to determine whether use of these drugs was associated with increased risk of OW/possible OW. Only 1 subject had a concomitant medication that was a CYP3A4 inhibitor (moderate).

Table 77: Cases of Investigator-Reported Opioid Withdrawal during Placebo-Controlled, Phase 3 Clinical Trials

Trial	Treatment Arm	Subject		AE Details			Baseline/Prior Opioid Use		COWS Score (max)	
		ID	Age(yrs)/Sex	Onset	Duration ¹	Severity	Disposition*	TDD-Opioid		Duration (months)
12-week (V9231/V9232)	Naldemedine (n=2)	12337-012	48/M	4	15	Mild	Completed	240	80.4	4
		12346-013	63/M	1	1	Moderate	Withdrawn	N/A	8.1	16
	Placebo (n=1)	12331-002	45/M	18	8	Mild	Withdrawn	390	39.0	15
52-week (V9235)	Naldemedine (n=11)	50402-004	45/F	42	7	Mild	Completed	48	1.1	9
		52219-001*	63/M	82	12	Mild	Completed	1260	68.8	5
		52229-001	47/F	2	8	Mild	Interrupted	36	34.1	9
		52311-003	67/F	1	2	Severe	Withdrawn	75	113.6	1
		52331-002	51/M	1	40*	Mild	Interrupted	400	50.4	1
	Placebo (n=7)	52356-014	57/M	3 81	13 14	Mild Mild	Withdrawn	360	82.2	7
		52361-011	54/F	3	4	Mild	Completed	30	9.2	1
		52375-003	57/F	1	11	Moderate	Withdrawn	360	132.1	8
		52399-004*	25/M	146	7	Moderate	Violation*	135	36.1	2
		52426-006	65/M	1	1	Moderate	Completed	90	73.5	1
Placebo (n=7)	52462-004	59/F	1	18	Moderate	Withdrawn*	240	89.9	1	
	52220-007	50/F	17	7	Moderate	Withdrawn	60	12.1	4	
	52331-001	56/M	2	109	Moderate	Withdrawn	1155	99.7	4	
	52367-001	60/M	3	8	Severe	Withdrawn	143	229.0	12	
	52368-026	42/M	1	1	Mild	Completed	84	3.7	5	
	52399-013*	26/F	133	22	Mild	Violation*	173	7.7	1	
	52428-013*	57/F	30	57	Moderate	Withdrawn*	128	107.9	9	
52450-004	58/F	35	1	Severe	Withdrawn	248	7.3	2		

(Source: Reviewer's figure)

Formula for calculation of AE duration: (AE stop date-AE start date) +1

Table 78: Cases of Possible Opioid Withdrawal in Placebo-Controlled, Phase 3 Clinical Trials, Identified by Retrospective Chart Review

Trial	Treatment Arm	Subject		AE Details				Baseline Opioid Use			COWS Score (max)
		ID	Age(yrs)/Sex	Symptoms	Onset* (Day)	Duration *	Severity	Disposition	Dose	Duration (months)	
12-week (V9231/V9232)	Naldemedine (n=7)	12205-004	64/M	GI only	1	57	Moderate	Completed	130	79.0	2
		12305-026	65/F	GI only	1	16	Mild	Withdrawn	45	2.2	2
		22326-002	46/M	GI+Non-GI	2	5	Moderate	Withdrawn	420	14.5	3
		22331-009	56/F	GI+Non-GI	4	88	Mild	Completed	75	32.6	4
		22344-007	63/F	GI+Non-GI	1	2	Moderate	Withdrawn	N/A	2.1	1
		22344-010	50/F	GI+Non-GI	1	3	Moderate	Withdrawn	120	135.6	3
		22350-005	48/M	GI only	1	10	Severe	Withdrawn	45	44.1	6
		12330-004	61/F	GI only	2	6	Moderate	Withdrawn	210	198.8	0
		22334-002	34/F	GI+Non-GI	73	3	Moderate	Completed	60	5.6	3
		22359-019	58/F	GI+Non-GI	25	38	Moderate	Withdrawn (unrelated)	95	82.0	1
52-week (V9235)	Naldemedine (n=14)	50303-001	47/F	GI+Non-GI	2	59	Mild	Completed	128	28.1	2
		52216-005	50/F	GI only	1	7	Moderate	Withdrawn	80	40.5	N/A
		52320-013	29/F	GI only	25	3	Moderate	Lost to follow-up after event	30	12.7	1
		52325-007	62/F	GI only	84	3	Mild	Completed	45	4.2	2
		52327-008	51/F	GI only	87	53	Mild	Withdrawn	40	121.5	3
		52333-001	47/F	GI+Non-GI	1	2	Mild	Withdrawn (unrelated)	30	71.5	3
		52355-009	52/F	GI only	3	20	Mild	Completed	180	119.8	2
		52361-008	59/F	GI+Non-GI	5	361	Moderate	Completed	45	5.0	4
		52404-003	48/F	GI only	3	1	Moderate	Withdrawn	60	27.9	0
		52413-001	60/F	GI+Non-GI	356	6	Mild	Completed	68	183.6	4
52421-004	78/M	GI only	4	3	Severe	Withdrawn	30	2.8	1		

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Trial	Treatment Arm	Subject		AE Details				Baseline Opioid Use		COWS Score (max)	
		ID	Age(yrs)/ Sex	Symptoms	Onset* (Day)	Duration *	Severity	Disposition	Dose		Duration (months)
		52427-006	50/M	GI only	38	5	Mild	Withdrawn	128	73.5	1
		52428-011	62/F	GI+Non-GI	1	1	Severe	Withdrawn	360	46.3	2
		52450-009	39/F	GI+Non-GI	1	1	Severe	Withdrawn	400	23.1	7
	Placebo (n=4)	52305-014	36/F	GI+Non-GI	11	5	Mild	Withdrawn	120	29.1	7
		52390-003	68/F	GI only	31	4	Mild	Completed	40	32.7	1
		52390-011	50/M	GI+Non-GI	3	5	Mild	Completed	100	113.1	1
		52398-006	45/M	GI+Non-GI	97	41	Severe	Completed	60	9.2	4

(Source: Reviewer's figure)

Formula for calculation of AE duration: (AE stop date-AE start date) +1

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Table 6. Key Characteristics of Investigator SMQ-Identified and Possible Opioid Withdrawal Events in Naldemedine Treated Subjects

SMQ-Identified N=15 events								
Onset Day				Relatedness	SMQ Terms			
D1	D2-<7	D 7-<30	D>30	Probable=12 Unlikely=2 Confounded=1	Drug Withdrawal Syndrome			
7	4	0	4					
Possible Opioid Withdrawal N=21 events								
Onset Day				Relatedness	GI only	nGI only	GI+nGI	
D1	D 2-<7	D 7-<30	D >30	Probable=20 Confounded=1	11	0	10	
9	7	1	4					

Reviewer: D=Day; GI=gastrointestinal; nGI=nonGI

For the cases of possible withdrawal, the symptoms occurring as part of these events include but were not limited to, hyperhidrosis, chills, increased lacrimation, hot flush/flushing, pyrexia, sneezing, feeling cold, abdominal pain, diarrhea, nausea, and vomiting.

DAAAP recommendation for labeling: The tables should include SMQ identified cases of opioid withdrawal and possible cases of opioid withdrawal in Symproic treated and placebo treated patients using the criteria defined in the protocols.

Overall, the incidence of opioid withdrawal and possible opioid withdrawal was low and generally consistent with other PAMORAs although there are limitations when comparing data among the other PAMORA studies due to different study designs, different types of opioid withdrawal analyses, and different criteria for the definition of an opioid withdrawal case. Therefore, although the overall incidence for OW in the other PAMORAs has been around 1-3%, all of these NDAs have used different criteria for determination of OW so comparison across NDAs is challenging. This NDA is the only PAMORA reviewed thus far by DAAAP that has incorporated Agency advice in the protocol designs and predefined analyses.

NOTE: It is challenging to compare the incidence of OW to other members of the PAMORA drug class because different programs used different methodologies. In addition, not all programs had prospective assessments.

8.5.2. Effects on Opioid Analgesia

The pharmacologic mechanism of PAMORAs relies on the absence of centrally-mediated pharmacological activity as a means to treat OIC without interfering with the analgesic effects of opioids. Therefore, evidence of reduced opioid analgesia due to naldemedine treatment would impact the overall benefit-risk assessment of this drug.

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Based on recommendations by the Agency, the Applicant used a multi-pronged approach to evaluate subjects' pain in the 3 placebo-controlled naldemedine clinical trials, including collection of total daily dose (TDD) of opioid (i.e., both maintenance and rescue doses), expressed in mg of morphine equivalents (ME), and scheduled pain assessments using the 11-point NRS, in addition to general adverse event reporting.

Opioid TDD (mg morphine equivalents)

Opioid dose data were calculated as follows:

- Average TDD of opioid for each time point was calculated as: (Total dose of opioid for each time point [every week for Studies V9231 and V9232 and every 4 weeks for Study V9235]) divided by (Number of days with available opioid data for each time point). For example, for Study V9235, the average TDD of opioid for every 4 weeks was calculated as: The total dose of opioid for every 4 weeks divided by (The number of days with available opioid data for every 4 weeks). The Total dose of opioid = total of ([number of days used] x [numeric frequency] x [equivalent morphine dose]). Average TDD at baseline was calculated similarly by replacing every 4 weeks with baseline period.
- Change in average TDD of opioid from baseline to each time point was defined as: (Average TDD of opioid for each time point) minus (Average TDD of opioid in baseline period)

The Applicant used opioid TDD data to identify "opioid outliers", which they defined as patients with change in TDD of $\geq 10\%$ or $\geq 30\%$ from baseline for at least one day during the Treatment Period. There were a number of problems with the Applicant's collection and analysis of opioid use data that affect the interpretation of the results. Opioid dose was to have been recorded daily by the patient. Summary statistics of average total daily and weekly dose of opioids and change from baseline by week were calculated by treatment group. For Studies V9231 and V9232, the following three types of opioid data were used by the Applicant for analysis: EDC (Electronic data capture) data, eDiary (electronic diary) data, and eDiary data without discrepant subjects (i.e., eDiary data excluding subjects who had discrepant data between EDC and eDiary data). The discrepant data were defined as the total daily dose (TDD) in eDiary data $> 200\%$ of EDC data for ≥ 5 days during the Treatment Period. The Applicant reported that the opioid data for subjects who met the criteria were reviewed by the medical team and the eDiary data without discrepant subjects were decided prior to unblinding. The analysis conducted using eDiary data without discrepant subjects was considered by the Applicant as the main analysis for determining TDD and change from baseline for Studies V9231 and V9232. For Study V9235, opioid analgesic data was captured using EDC only. Prior and concomitant medications were recorded on the eCRF (electronic Case Report Form) for all three studies.

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Unfortunately, the accuracy of these outlier data was questioned due to the high rate of discrepancies found between patient-reported and investigator-reported opioid doses, as well as atypical dose fluctuation patterns suggesting incomplete patient records. In an effort to address this issue, the Applicant identified a group of discrepant subjects with inconsistencies in doses reported during the treatment period and conducted post-hoc analyses excluding these subjects. However, use of a definition inclusive of any subject with a single outlying dose carries a high risk of over-identification of subjects, even with the Applicant's strategy to identify discrepant subjects. In addition, patients with discrepancies in baseline opioid doses were not flagged as discrepant subjects. Therefore, calculations of changes in TDD using these baseline data were generally considered unreliable.

It is also important to note that the ranges used for opioid dose strata (i.e., 30 to 100 mg and >100 mg), as well as the criteria to define opioid outliers (i.e., increase in TDD $\geq 10\%$ and $\geq 30\%$ from baseline), were arbitrary cut-off values without clear rationale or known clinical significance. Furthermore, the range of baseline opioid TDDs was wide, and a dose increase of 10% or 30% in patients with relatively low baseline TDD would likely have a different clinical significance than those with the highest baseline TDD who are more likely to have unstable pain, be on multiple opioids, and require additional increases in opioid dose over time.

Nevertheless, these cut-offs were considered reasonable to provide a general sense of the number of patients who required an increase in opioid dose for a general assessment of treatment differences and to describe overall trends in opioid usage.

Study V9231:

- Mean baseline TDD of opioid was lower in the naldemedine group (approximately 125 mg ME), compared to placebo (approximately 140 mg ME). This difference between groups was driven by a few outliers in the placebo group receiving an opioid ME >400 mg, and no difference was observed between groups when the mean daily dose at baseline was calculated for subjects taking up to 400 mg. Therefore, this difference between group means was not considered clinically significant, and is supported by similarities in median doses and distributions between groups.
- Overall, opioid medication regimens were similar between groups. For both groups, the most commonly reported opioid analgesic was hydrocodone/APAP [Vicodin] (30% naldemedine and 26% placebo).

Study V9232:

- Mean baseline TDD of opioid was approximately 118 mg ME in the naldemedine group and 124 mg ME in the placebo group.
- Sixty-one percent of the patient population was in the lower opioid dose group (30-100 mg ME) vs. 40% in the higher dose group (>100 mg ME). Both strata contained the same number of subjects from each treatment arm.

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- The most common opioid medication was hydrocodone/APAP [Vicodin] (32% naldemedine and 33% placebo).

Study V9235:

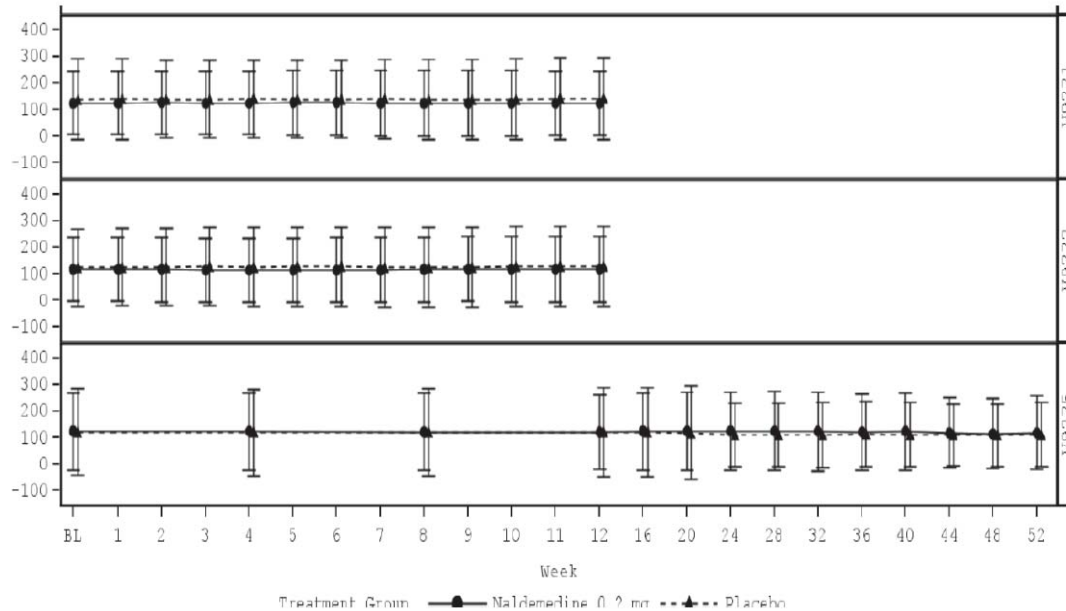
- Mean baseline TDD of opioid was 123 mg ME in the naldemedine group and 121 mg ME in the placebo group.
- There were 64% naldemedine and 63% placebo in the 30-100 mg group; 36% naldemedine and 37% placebo were in the >100 mg ME group.
- The most commonly reported opioid was hydrocodone/APAP [Vicodin] (36% and 39% naldemedine and placebo, respectively).

In general, there were no major differences in the percent of outliers in the naldemedine group compared to placebo. During Study V9231, 195 (78%) subjects in the naldemedine arm and 196 (79%) subjects in the placebo arm who had $\geq 10\%$ increase in TDD of opioid, and 153 (61%) naldemedine subjects in the naldemedine arm and 161 (65%) subjects in the placebo subjects had $\geq 30\%$ increase in TDD. During Study V9232, 185 (74%) subjects in the naldemedine and 176 (70%) subjects in the placebo arm had $\geq 10\%$ increase in TDD of opioids, and 143 (57%) subjects in the naldemedine and 138 (54%) subjects in the placebo arm had $\geq 30\%$ increase in TDD. These tabulations include all subjects with any dose (≥ 1 TDD) meeting these cut-offs, which explains the high incidence in both arms and both studies.

However, mean TDD of opioid analgesics remained generally unchanged relative to baseline values in both treatment groups. Relatively minor differences in total weekly dose may have been observed between naldemedine and placebo, but these differences, overall, were minimal and are not considered clinically meaningful. When stratified by opioid dose ranges, the highest dose group was the only group with increased mean TDD of opioid. (Figure 37)

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Figure 35: Average Total Daily Dose of Opioid by Study and Time Point (Mean±SD) Phase 3 Studies V9231, V9232, and V9235 (Top to Bottom)



Applicant's Figure 9-9, Integrated Summary of Safety; p. 457

11-Point NRS Scores

Pain assessments were conducted at baseline and clinical trial visits using the 11-point NRS instrument. A pre-specified definition of change in NRS score ≥ 2 was used to define a group of outliers.

However, these data were considered only minimally useful to assess the adequacy of patients' pain control over time. Numeric pain scales provide a snapshot of patients' pain at a particular moment. Because pain severity typically fluctuates and can be affected by numerous intrinsic and extrinsic factors, including timing of assessment with respect to analgesic medications, frequent assessments are needed to obtain meaningful data of pain control over time. Ideally, NRS scores should have been obtained daily, along with other patient-reported diary day, including records of daily opioid use.

Overall, these data are not suggestive of a difference in analgesia between groups, and findings are consistent with other pain assessments across all clinical trials. However, these data need to be interpreted cautiously due to their limited inherent meaningfulness.

Discussion

Overall, pain-related assessments did not suggest a significant impact of naldemedine treatment on opioid analgesia. However, studies were adequately designed to conclusively

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evaluate for treatment effect, due to infrequent NRS scores and errors in opioid dose data collection. In addition, study discontinuations due to perceived reduction in opioid efficacy indicate that naldemedine could interfere with opioid analgesia in some patients. Therefore, conclusions must be interpreted with caution given the limitations in data collection of opioid dose data and collected opioid dose data.

Antagonism of opioid-mediated analgesia raises concern for drug penetration of the blood brain barrier. Similar concerns are also raised in cases of centrally-mediated manifestations of opioid withdrawal. For this reason, cautious use in patients with conditions that decrease the integrity of the blood brain barrier is recommended. In naldemedine clinical trials, the number of patients with these conditions is too small to evaluate this risk. However, most patients reporting increased pain or OW did not have such conditions or other identifiable risk factors.

Although the analgesic response to opioids is generally considered a centrally-mediated process, opioids also have peripheral analgesic effects mediated by μ -opioid receptors in spinal nerve roots, various peripheral nerves (e.g., sciatic nerve), skin, etc. This may explain the reduction in opioid-mediated analgesia by peripherally restricted receptor antagonists. Furthermore, central effects may occur indirectly as a result of peripheral mediation of the neural pathways via efferent input across the blood brain barrier. Therefore, these drugs may be able to cause centrally mediated effects without penetration into the CNS. [10]

Overall, the percentage of clinical trial patients with increased pain with naldemedine was small, and few required intervention such as opioid dose escalation or naldemedine treatment discontinuation/interruption. Therefore, this reviewer does not recommend the need for preemptive, empirical opioid dosage adjustment when initiating naldemedine treatment. Even if a group of highly susceptible patients is identified, any potential benefit of preemptive dose escalation would not justify exposing patients to the possible risk of opioid overdose conferred by preemptive dose escalation.

8.5.3. Major Adverse Cardiac Events (MACE)

Concern for the CV safety of the PAMORA drug class originates from OIC clinical trial data of Entereg (alvimopan) demonstrating a higher rate of MACE compared to placebo without baseline differences in CV risk between treatment arms. The most compelling finding was the occurrence of 7 MIs (2 fatal) in the Entereg group vs. 0 in the placebo group. Based on these data, the use of Entereg was subsequently approved only for management of post-operative ileus, with restricted use of 7 days maximum (15 doses) administered only in the inpatient setting and under a REMS.

Although a similar MACE safety signal was not identified with either of the PAMORAs with approved OIC indications, premarketing safety data were not adequate to detect an increased risk of MACE. For Relistor, only 4 weeks of controlled safety data were obtained during clinical

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trials, and evaluation of long-term safety data were from an uncontrolled, single-arm extension trial. Therefore, evaluation of MACE risk with Relistor has been limited and based on retrospective review of primarily uncontrolled data. For Movantik, long-term safety data were obtained from a 52-week, controlled trial with prospective adjudication for MACE. Although an increased rate of MACE was not observed in Movantik-treated subjects, this trial was not a formal CVOT or enriched for high-risk patients and did not have a large enough study population to detect a treatment-related increase in MACE risk.

In June 2014, a meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) was held, with DGIEP and several stakeholders in attendance, to address the risk and need for clinical trial safety evaluation of MACE for the PAMORA drug class. The majority opinion was that the Entereg data represented a valid safety concern, but there was less agreement whether this represented a class-wide safety concern. The committee also had split opinions regarding the clinical trial safety data needed to evaluate this risk, though most committee members who recommended additional data collection felt that a premarketing CVOT should not be required and a post-marketing observational study would be sufficient.

Therefore, it remains unclear whether this represents a class-wide safety signal. For Relistor and Movantik, there were PMRs to evaluate MACE risk in observational, epidemiologic studies. At this time, these studies are currently ongoing and no results from these studies are available for review.

Biological Plausibility of MACE Risk

Although the pharmacological activity of PAMORAs predominantly occurs via antagonism of μ -opioid receptors, these drugs also have variable binding affinities for the other opioid receptor subtypes. There is evidence that opioids have cardioprotective effects mediated through activation of delta (δ)-opioid receptors, leading to increased myocardial tolerance to ischemia (i.e., pre-ischemic conditioning). Endogenous opioids (EOPs) are released in response to ischemic injury.[REF] Antagonism of δ -opioid receptors has been proposed as a possible mechanism contributing to an increased risk of MACE with PAMORAs. In addition, differences in binding affinities for and agonist/antagonist properties at the δ -opioid subtype have been cited as evidence to suggest variability in MACE risk within the drug class.

This widespread distribution and localization of EOPs throughout the cardiovascular system exerts biological activities which influence and regulate cardiovascular functions, both centrally and peripherally, including direct action of EOP on the heart

Table 79: Relative Affinities for Opioid Receptor Subtypes for Members of the PAMORA Subclass and Related Opioids

	Receptor Affinities (K _i) Ratio (μ : δ : κ)
Naldemedine	1 : 1.3 : 3
Entereg (alvimopan)	1 : 23 : 227
Relistor (methylnaltrexone)	1 : 135 [†] : 5
Movantik (naloxegol)	1 : 27 : 1.2 [†]
Naloxone	1 : 13 : 3
Naltrexone	1 : 6 : 8
Morphine	1 : 50 : 176
Meperidine	1 : 11 : 13

(Source: AC Background package,)

[†]Indicates agonist activity: Relistor has partial agonist activity at the δ-opioid receptor subtype, and naloxegol has partial agonist activity at the κ-opioid receptor subtype

Increased myocardial oxygen demand due to physiological stress of opioid withdrawal or drug-induced vascular effects has also been raised as a possible mechanism of increased CV risk due to PAMORA treatment. However, no overlap between CV events and opioid withdrawal or blood pressure changes has been identified from safety data to support this hypothesis.

In the consultation memo by the Division of Cardiovascular and Renal Products (DCRP), submitted on 07 April 2014, under NDA 204760, three major mechanisms of drug-related adverse CV outcomes are described:

- Syndromes of increased vasomotor tone: Effects would include elevations of systemic blood pressure and coronary vasospasm. The DCRP reviewer noted that, in classes of drugs that can cause vasospasm, i.e., anti-migraine triptans, angina appears much more common than myocardial infarctions. In the Entereg clinical, 3 AEs of unstable angina were noted in the treatment group (vs. 0 in placebo), and in the open-label MNTX study 3358, one patient experienced an SAE of vasospastic angina and subsequently had ergonovine-induced coronary vasospasm in the catheterization laboratory involving the LAD and CFX coronary arteries that was reversed with 1000 mcg of IC nitroglycerin.
- Drug induced electrical instability/repolarization abnormalities: There has been no evidence of drug-induced proarrhythmic ECG changes for any of these drugs.

This reviewer notes, however, that both nonclinical and clinical studies conducted

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specifically to assess the arrhythmogenic potential of these drugs were conducted in healthy individuals and animals who were not receiving concomitant opioid medication. Under normal circumstances, physiological effects of opioid antagonists are virtually non-detectable because, with the exception of some hormonal effects, most of the systems mediated are usually not tonically active. Therefore, reversal or inhibition of these systems will have little physiological effect. (Dr. Pasternak) In addition, there are data to suggest a protective role of opioids against cardiac arrhythmias caused by ischemia.

- Prothrombotic effects: Although not systematically assessed, an increased risk of thrombotic effects has not been observed with these drugs.

Therefore, in addition to a review of CV events meeting the regulatory definition of MACE (i.e., myocardial infarction, stroke, and cardiovascular death), other CV-related events were reviewed to identify a pattern that would fitting any these mechanisms.

It is also noted that prevalence of cardiovascular disease and risk factors in the study populations enrolled in PAMORA OIC trials has been higher than the general American population. There are data suggesting that chronic opioid exposure is associated with increased cardiovascular disease. Therefore, uncontrolled data need to be evaluated cautiously.

Clinical Trial Data for MACE and Other CV Events

MACE was defined as CV death, MI, and cerebrovascular accident (stroke). An external independent CAC consisting of experienced cardiologists was established to provide blinded medical review and adjudicate all events known or suspected to be a MACE.

Pre-specified criteria were used to identify possible CV cases based on adverse events, clinical laboratory evaluations, physical examinations, and ECGs. Results from COWS, SOWS, and 11-point NRS assessments were also reviewed. Cases confirmed as CV events were sent for adjudication by the independent CAC.

CV events for 66 subjects in the phase 3 safety population (31 subjects in the naldemedine arm and 35 subjects in the placebo arm) were sent to the CAC for review (Figure 35). In total, 11 cases were adjudicated as MACE—5 in the naldemedine arm and 6 in the placebo arm. Nine of the 11 cases occurred during Study V9235.

Figure 36: Cases Flagged and Adjudicated for MACE Evaluation

	<u>Study V9231</u>		<u>Study V9232</u>		<u>Study V9235</u>	
	<u>Naldemedine</u>	<u>Placebo</u>	<u>Naldemedine</u>	<u>Placebo</u>	<u>Naldemedine</u>	<u>Placebo</u>
Events Flagged as Possible CV Event	23 (8.5%)	11 (4.0%)	14 (5.2%)	17 (6.2%)	20 (3.2%)	26 (4.2%)
Events Sent to CAC for Adjudication	5 (1.8%)	2 (0.7%)	6 (2.2%)	7 (2.6%)	20 (3.2%)	26 (4.2%)
Events Adjudicated as MACE	1 (0.4%)	0	0	1 (0.4%)	4 (0.6%)	5 (0.8%)

(Source: Reviewer's figure based on data provided by the Applicant)
 Abbreviations used in figure: CAC, ; CV, ; MACE

Table 80: Cases of MACE by CAC Adjudication

	Naldemedine (N=1163)	Placebo (N=1165)	Overall (N=2328)
All MACE	5 (0.4)	6 (0.5)	11 (0.5)
CV death	1 (0.1)	3 (0.3)	4 (0.2)
Myocardial Infarction	3 (0.3)	3 (0.3)	6 (0.3)
CVA	1 (0.1)	0	1 (<0.1)

(Source: Reviewer's table)

A total of 9 deaths occurred in controlled phase 3 trials (see Section 8.4.1). Six deaths were due to unwitnessed cardiac/cardiopulmonary arrests. In all cases of sudden death, a presumptive cause of death was listed on the death certificate. None of the diagnoses were supported by data from clinical investigation or post-mortem evaluation.

- Subject 22359-018 (naldemedine, 37-year-old female)- presumptive diagnosis of opioid overdose
- Subject 52352-002 (placebo, 52-year-old male)- presumptive diagnosis of opioid overdose
- Subject 52375-007 (naldemedine, 53-year-old female)- presumptive diagnosis of cerebrovascular accident
- Subject 52437-005 (placebo, 64-year-old male)- presumptive diagnosis of cardiac arrest
- Subject 52449-005 (naldemedine, 49-year-old male)-, presumptive diagnosis of myocardial infarction

There were no data were available to support the cause of death for any of these cases, and it appears that CAC adjudication relied upon these unsubstantiated causes of death, particularly

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for the presumed cases of opioid overdose, neither of which had available toxicology data.

In addition, the CAC inconsistently adjudicated deaths with presumed cause of death due to a MACE—e.g., an unwitnessed death of a 49-year-old female, presumed due to complications of arteriosclerosis, was adjudicated as “cardiovascular death”, while an unwitnessed death in a 53-year-old female, given a presumptive diagnosis of cerebrovascular event, was adjudicated as “undetermined cause.” No distinguishing factors (e.g., risk factors, medical history, demographics) could be identified to explain the difference in adjudication.

Therefore, all deaths with unsubstantiated diagnoses assigned by the coroner are considered possible MACE by this reviewer and are included as possible CV deaths. Separate tabulations are shown for adjudicated cases of MACE and other cases included by this reviewer.

Overall, the clinical trial data are not suggestive of an increased risk of MACE with naldemedine treatment. However, the safety database is not adequate to evaluate for rare events. [11]

In the absence of a clear MACE safety signal, the available premarketing data are considered adequate to support marketing approval. However, these data are not sufficient to exclude an increased risk of MACE ~1.8- to 2-fold above the general population (see the confidence intervals in Table 73), which is generally considered the maximum acceptable hazard ratio (i.e., acceptable level of MACE risk with exposure to treatments of non-life-threatening conditions). Therefore, a requirement to obtain post-marketing data for further assessment of MACE risk will be issued for this drug. (See section 12)

Table 81: Subjects with Adjudicated or Possible MACE in Phase 3, Placebo-Controlled Naldemedine Clinical Trials

CAC Review		Subject		Type of Event			AE Onset		Reviewer Comment (Abbreviated)*	
Reviewed? (Yes/No)	MACE? (Yes/No)	Subject ID	Treatment	Age(yrs)/Sex	Outcome (Fatal/Non-fatal)	AE Term(s)	CAC Assessment	Relative Study Day		TEAE (Yes/No)
YES	Yes	12322 - 008	Naldemedine	65/F	Non-fatal	SVT (with cardiac ischemia)	MI (type 2)	19	Yes	Agree with CAC
	Yes	52319-037	Naldemedine	59/M	Non-fatal	Acute MI	MI	82	Yes	Agree with CAC
	Yes	52335-012	Naldemedine	53/F	Non-fatal	Acute MI	MI	228	Yes	Agree with CAC
	Yes	52442-021	Naldemedine	52/F	Non-fatal	CVA	CVA	245	Yes	Agree with CAC
	Yes	52449-005	Naldemedine	49/M	Fatal	Presumed MI; Sudden death	Cardiovascular death	346	UNK* (Yes)	- Unwitnessed event, presumptive diagnosis - No clinical data to support diagnosis Possible MACE
Yes	22324-008	Placebo	44/M	Non-fatal	Syncope, hypotension, altered mental status	MI (type 2)	18	Yes	ECG and laboratory data consistent with MI Agree with CAC	
Yes	52319-017	Placebo	63/F	Non-fatal	Angina Unstable	MI	246	Yes	Agree with CAC	
Yes	52363-013	Placebo	59/M	Non-fatal	Acute MI	MI	119	Yes	Agree with CAC	
Yes	52437-005	Placebo	64/M	Fatal	Cardiac arrest	Cardiovascular death	28	Yes	- Unwitnessed event, presumptive diagnosis - No clinical data to support diagnosis Possible MACE	
Yes	52442-017	Placebo	49/F	Fatal	Arteriosclerosis	Cardiovascular death	31	Yes	Unwitnessed event, presumptive diagnosis	

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CAC Review		Subject		Type of Event			AE Onset		Reviewer Comment (Abbreviated)*	
Reviewed? (Yes/No)	MACE? (Yes/No)	Subject ID	Treatment	Age(yrs)/Sex	Outcome (Fatal/Non-fatal)	AE Term(s)	CAC Assessment	Relative Study Day		TEAE (Yes/No)
										- No clinical data to support diagnosis Possible MACE
	Yes	52446-013	Placebo	78/F	Fatal	CVA	Cardiovascular death	175	Yes	- Diagnosis of CVA confirmed by imaging Possible MACE
	No	22359-018	Naldemedine	37/F	Fatal	Presumed overdose; Cardiopulm. arrest (sudden death)	Non-cardiac death	9	Yes	- Unwitnessed event, presumptive diagnosis - No clinical data to support diagnosis MACE cannot be ruled out (Possible MACE)
	No	52415-004	Naldemedine	52/F	Non-fatal	Myocardial infarction	Non-event	72	Yes	- MI diagnosed by cardiac catheterization - Hospitalized with multiple SAEs Consistent with MACE
	No	52375-007	Naldemedine	53/F	Fatal	Suspected CVA (sudden death)	Undetermined cause of death	350	UNK* (Yes)	- Unwitnessed event, presumptive diagnosis - No clinical data to support diagnosis MACE cannot be ruled out (Possible MACE)
	No	52352-002	Placebo	52/M	Fatal	Presumed overdose; Cardiopulm. arrest (sudden death)	Non-cardiac death	50	UNK* (>7 days)	- Unwitnessed event, presumptive diagnosis - No clinical data to support diagnosis MACE cannot be ruled out (Possible MACE)

(Source: Reviewer's table)

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* The last day of study drug administration is not known for these 3 subjects because the study medication bottles were not returned to the clinical site for accountability. Therefore, the Investigator imputed the date of last study drug administration as the last date confirmed by the clinical trial site, which was the last dose prior to the subject's last visit. However, a new supply of study medication would have been dispensed at that visit, and the Investigator acknowledged that these 3 subjects were active clinical trial participants at the time of death. Because the imputed date of last study drug administration is likely incorrect, the determination whether these events are treatment-emergent is unreliable. Assuming regular treatment compliance, these 3 events would all be treatment-emergent (<14 days after last dose) based on the subject's last study visit, and only Subject 52352-002 would likely have been off-treatment due to missed visit 7 days prior to death.

Table 82: Relative Risk Calculations for Adjudicated and MACE and Possible MACE Cases

Event Definition	Datasets used for Analysis			Number of Events		Relative Risk	Statistics	
	Population (Studies)	Denominator	Treatment Arm	Events, n Per Arm	95% Confidence Interval			
					Lower Bound		Upper Bound	
CAC-adjudicated MACE	All phase 3 (n=11)	Patient-years	Naldemedine	5/605	0.835	0.256	2.720	
		N Subjects	Placebo	6/606				
	V9235 only (n=9)	Patient-years	Naldemedine	5/1163	0.835	0.256	2.728	
			Placebo	6/1165				
		N Subjects	Naldemedine	4/490	0.835	0.255	2.725	
			Placebo	5/490				
CAC-adjudicated MACE + all sudden deaths	All phase 3 (n=14)	Patient-years	Naldemedine	4/621	0.800	0.216	2.961	
		N Subjects	Placebo	5/619				
	V9235 only (n=11)	Patient-years	Naldemedine	7/605	1.002	0.353	2.838	
			Placebo	7/606				
		N Subjects	Naldemedine	7/1163	1.002	0.352	2.847	
			Placebo	7/1165				
N Subjects	Naldemedine	5/490	0.833	0.256	2.713			
	Placebo	6/490						
N Subjects	Naldemedine	5/621	0.831	0.255	2.708			
	Placebo	6/619						

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Event Definition	Datasets used for Analysis			Number of Events		Statistics		
	Population (Studies)	Denominator	Treatment Arm	Events, n Per Arm	Relative Risk	95% Confidence Interval		
						Lower Bound	Upper Bound	
CAC-adjudicated MACE + all sudden deaths+ reviewer-identified case	All phase 3 (n=15)	Patient-years	Naldemedine	8/605	1.145	0.418	3.137	
		N Subjects	Placebo	7/606				
	V9235 only (n=12)	Patient-years	Naldemedine	8/1163	1.145	0.416	3.147	
		N Subjects	Placebo	7/1165				
		Patient-years	Naldemedine	6/490	1.000	0.325	3.079	
		N Subjects	Placebo	6/490				
			Naldemedine	6/621	0.997	0.323	3.073	
			Placebo	6/619				

(Source: Reviewer's Table)

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Narratives for Events in Table 72 (in order by Subject ID within each treatment group)

Naldemedine (n=8)

- Subject 12322-008: Adjudicated as MACE (myocardial infarction, type 2)
65-year-old female SAE of SVT with secondary myocardial ischemia, identified by the CAC
- Subject 22359-018: Adjudicated as non-cardiovascular death
37-year-old female with an unwitnessed cardiopulmonary arrest, resulting in global cerebral hypoxic injury and death after withdrawal of care; the event was attributed to opioid overdose based on subject's prior history of overdose and opioid use, but was not substantiated by clinical data or post-mortem evaluation; of note, no diagnostic toxicology studies were obtained in the hospital. Compared to other subjects with fatal events during study participation, this subject was relatively young but had cardiovascular risk factors including obesity, hypertension, and chronic opioid use.
- Subject 52319-037: Adjudicated as MACE (myocardial infarction)
59-year-old male with non-fatal myocardial infarction, presenting with chest pain/pressure radiating to his jaw, associated with nausea, palpitations, and diaphoresis; ECG with ST elevation suggestive of acute myocardial infarction and elevated troponin; treatment with aspirin, heparin, ondansetron, and carvedilol; then heart catheterization with stent of the left circumflex artery
- Subject 52335-012: Adjudicated as MACE (myocardial infarction)
53-year-old female with non-fatal myocardial infarction
- Subject 52375-007: Adjudicated as undetermined cause of death
53-year-old female with unwitnessed death (cardiopulmonary arrest), which was assigned a presumptive diagnosis of cerebrovascular accident, though no post-mortem evaluation was performed, and no clinical data were available to support this diagnosis. On this basis, this reviewer understands the rationale for the adjudication of "undetermined cause of death" by the CAC, but notes that this adjudication is not consistent with other unwitnessed fatalities.
- Subject 52415-004: Adjudicated as non-cardiovascular event
52-year-old male who presented on Study Day 72 with chest pain and shortness of breath, and notable findings of pleural and pericardial effusions and abnormal ECG; diagnosis of adenocarcinoma of the lung was made based on pleural fluid sample with malignant cells; found to have DVT, PE, and cardiomegaly; myocardial infarction was diagnosed based on u ECG abnormalities and findings of ischemia and blockage on cardiac catheterization
Reviewer comment: During the hospital admission from Day 72 to 74, the subject had 4 reported SAEs of adenocarcinoma, deep venous thrombosis, pulmonary embolism, and myocardial infarction, of which only myocardial infarction is under consideration as MACE. For unknown reason, this event was not sent to the CAC for adjudication. Based on the pre-specified criteria for identification of possible MACE events for adjudication, both the AE of

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myocardial infarction and the cardiac catheterization would have qualified this event for adjudication. This reviewer agrees that the subject's death due to the TEAE of adenocarcinoma is not MACE, and the events of PE and DVT are unlikely MACE.

- Subject 52442-021: Adjudicated as MACE (cerebrovascular accident)
52-year-old female with a CVA
- Subject 52449-005: Adjudicated as MACE (cardiovascular death)
49-year-old male with unwitnessed death (cardiac/cardiopulmonary arrest), assigned a presumptive diagnosis of myocardial infarction due to or as a consequence of diabetes, although no post-mortem evaluation was performed, and no clinical data were available to support this diagnosis

Placebo (n=7)

- Subject 22324-008: Adjudicated as MACE (myocardial infarction, type 2)
44-year-old male with SAE of "syncope" due to hypotension/hypovolemia with organ dysfunction due to hypoperfusion, including myocardial ischemia, determined by the CAC to be consistent with a myocardial infarction, type 2
- Subject 52319-017: Adjudicated as MACE (myocardial infarction)
63-year-old female with event of unstable angina with radiating chest pain, identified by the CAC as a myocardial infarction, for which the subject underwent left heart catheterization, coronary angiogram and balloon and stent placement to the obtuse marginal and right coronary artery.
- Subject 52352-002: Adjudicated as non-cardiovascular death
52-year-old male with unwitnessed death (cardiopulmonary arrest), which was assigned a presumptive diagnosis of overdose based on the subject's history of opioid use; no post-mortem evaluation was performed, and no clinical data were available to support this diagnosis.
- Subject 52363-013: Adjudicated as MACE (myocardial infarction)
59-year-old male with myocardial infarction, presenting with substernal chest pain on with exertion, radiating down left arm, associated with shortness of breath; Troponin was markedly elevated, and cardiac catheterization showed variable degrees of stenosis of the right coronary artery (RCA), posterior descending artery, and left anterior descending (LAD) artery, and circumflex artery; a drug-eluting stent was placed in the LAD artery
- Subject 52437-005: Adjudicated as MACE (cardiovascular death)
64-year-old male with unwitnessed arrest resulting in death after unsuccessful cardiopulmonary resuscitation; no post-mortem evaluation was performed, and no clinical data were obtained to confirm the cause of death
- Subject 52442-017: Adjudicated as MACE (cardiovascular death)

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49-year-old female with unwitnessed death (cardiopulmonary arrest), which was assigned a presumptive diagnosis of cardiac arrest due to complications of atherosclerotic heart disease, although no post-mortem evaluation was performed, and no clinical data were available to support this diagnosis

- Subject 52446-013: Adjudicated as MACE (cardiovascular death)
78-year-old female with CVA due to occlusive basilar thrombosis, confirmed by radiologic studies, with fatal outcome following failed thrombectomy procedure

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Figure 37: Non-MACE Cardiac and Vascular Adverse Events in Phase 3 Clinical Trials

Category	Adverse Event	V9231&V9232		V9235		TOTAL	
		Naldemedine	Placebo	Naldemedine	Placebo	Naldemedine	Placebo
Cardiovascular/ Arterial	Angina	0	1	1	7	1	8
	Acute coronary syndrome	0	0	0	1	0	1
	Arteriosclerosis, NOS	0	0	0	1	0	1
	Arterial aneurysm	0	0	2	0	2	0
	Blood pressure fluctuation	0	0	0	1	0	1
	Blood pressure elevated	7	1	11	13	18	14
	Carotid artery arteriosclerosis	0	0	0	1	0	1
	Carotid artery stenosis	0	0	1	0	1	0
	Femoral artery occlusion	0	0	1	0	1	0
	Hepatic artery stenosis	0	0	1	0	1	0
	Peripheral arterial disease	0	0	3	1	3	1
	Peripheral artery restenosis	0	0	0	1	0	1
	Total		7	2	20	26	27
Cardiac	Aortic valve incompetence	0	0	0	1	0	1
	Atrial dilatation, left	0	0	0	1	0	1
	Cardiomegaly	0	0	1	0	1	0
	Congestive heart failure	2	0	3	3	5	3
	Mitral valve regurgitation	0	0	0	2	0	2
	Troponin (cardiac) increased	1	0	0	0	1	0
	Total		3	0	4	7	7
Vascular- Venous	Deep venous thrombosis	0*	0	1	1	1*	1
	Pulmonary embolism	0	0	2	0	2	0
	Thrombophlebitis	0	0	1	0	1	0
	Thrombosis Lower Leg (NOS)	0	0	1	0	1	0
	Venous insufficiency	0	1	1	0	1	1
	Total	0*	1	6**	1	6**	2

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Category	Adverse Event	V9231&V9232		V9235		TOTAL	
		Naldemedine	Placebo	Naldemedine	Placebo	Naldemedine	Placebo
Cardiac Rhythm/ Conduction	Atrial fibrillation	0	0	4	2	4	2
	AV block, First degree	0	0	0	1	0	1
	Bradycardia	0	0	1	1	1	1
	Bundle branch block	0	0	0	3	0	3
	Extrasystoles, NOS	0	0	1	0	1	0
	Palpitations	1	0	2	2	3	2
	Sick sinus syndrome	0	1	0	0	0	1
	Supraventricular arrhythmia, NOS	0	0	0	1	0	1
	Supraventricular extrasystoles	0	0	1	0	1	0
	Supraventricular tachycardia	1	0	0	0	1	0
	Tachycardia	2	1	3	1	5	2
	Ventricular extrasystoles	1	0	2	0	3	0
	Total		5	2	14	11	19
ECG Investigations	Abnormal ECG, NOS	1	0	1	1	2	1
	QRS prolonged	0	0	1	0	1	0
	QT prolonged	0	0	0	2	0	2
	T wave abnormal	1	0	2	1	3	1
	Total	2	0	4	4	7	4
Neurologic/ Neurovascular	Convulsion	0	1	2	0	2	1
	Loss of consciousness	0	0	1	0	1	0
	Presyncope	1	0	0	3	1	3
	Syncope	1	2	3	1	4	3
	Transient ischemic attack	0	0	0	1	0	1
Total	2	3	6	5	8	8	

(Source: Reviewer's Table)

Abbreviations in table: ECG, electrocardiogram; NOS, not otherwise specified

* Deep venous thrombosis with AE Onset >14 days post-treatment (n=1)

** 1 subject with concurrent pulmonary embolism and deep venous thrombosis, included in both tabulations

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Difference in rhythm/conduction is due to increased tachycardia, palpitations. Some of these cases were associated with other AEs of opiate withdrawal or dehydration. These do not appear to be independent safety findings.

This reviewer concludes that no evidence exists evidence to support a direct cause by any of the types of mechanisms. However, evaluation for an adverse effect due to antagonism of the δ -opioid receptor is challenging. The physiologic response to myocardial ischemia is complex, and the relative contribution of δ -opioid receptor pathways is not known. In addition, interference with the proposed cardioprotective effect does not suggest that opioid antagonists would directly precipitate cardiac events, but instead may increase the risk of myocardial injury when faced with an ischemic insult/challenge, making adverse treatment effects more difficult to detect.

8.6. Specific Safety Studies/Clinical Trials

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

No special cancer-related assessments with conducted with naldemedine. No specific safety concerns were identified from either nonclinical studies or clinical trials to indicate the need for special assessments. In addition, formal nonclinical carcinogenicity studies were negative. For these studies, both the protocols and study results were reviewed by the carcinogenicity nonclinical review team.

8.7.2. Human Reproduction and Pregnancy

No assessments of human reproduction and pregnancy have been conducted with naldemedine. In all clinical trials, pregnancy and lactation were exclusion criteria, and use of contraception was a requirement for participation. Of note, one female subject was withdrawn from study participation due to pregnancy but was in the placebo arm and not exposed to naldemedine.

8.7.3. Pediatrics and Assessment of Effects on Growth

Not applicable

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Naldemedine is a derivative of naltrexone, which, in turn, is a derivative of thebaine, a Schedule II opium derivative. As a derivative of thebaine, naldemedine was classified as a Schedule II

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substance. As part of the NDA, the Applicant submitted a request to decontrol naldemedine from the Controlled Substances Act (CSA) on the basis that naldemedine has no abuse potential.

To support this conclusion, the Applicant submitted data from a thorough abuse assessment, including three studies conducted in animals. Based on these data, the CSS staff concluded that naldemedine does not have abuse potential. For a detailed review of the assessment for abuse potential, the reader is referred to the CSS memo submitted by Katherine Bonson, dated 18 January 2017.

The following are the major findings that contributed to the CSS staff's assessment:

- *In vitro* receptor binding studies demonstrate that naldemedine and its major metabolites have high affinity for mu, kappa and delta opioid receptors, and both the parent drug and metabolites act as an opioid antagonist at all receptor subtypes. Opioid antagonists are not associated with abuse potential.
- *In vitro* receptor binding studies demonstrated no off-target binding of naldemedine or its metabolites at sites associated with abuse potential.
- *In vivo* receptor binding studies in animals show limited binding of naldemedine at mu opioid receptors in the cerebral cortex and thalamus. Similarly, brain penetration studies with acute and chronic administration of radiolabeled naldemedine in animals showed minimal penetration of naldemedine into the CNS. These data suggest naldemedine is unlikely to cross the blood-brain barrier in humans, and is unlikely to block the activity of centrally-acting mu-opioid agonists administered to treat pain.
- Naldemedine did not produce any abuse-related behaviors during a general observational study in animals, using a standardized list of behaviors.
- Data from a self-administration study in animals suggests that naldemedine does not have rewarding properties.
- In a drug discrimination study in animals, naldemedine did not generalize to morphine, suggesting that naldemedine's action at opioid receptors does not have an agonistic component.
- In physical dependence studies in animals, chronic administration of naldemedine did not produce opioid-like withdrawal effects following drug discontinuation. Furthermore, when animals that were physically dependent on opioids were given naldemedine, the drug precipitated peripherally-associated withdrawal signs but no CNS-associated signs. These data demonstrate that pharmacological activity of naldemedine is restricted to peripheral effects.
- In clinical safety and efficacy studies, few CNS-associated AEs were reported and had occurred at similar rates as placebo.

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This reviewer agrees with the CSS team’s assessment that clinical trial data do not suggest an abuse potential of naldemedine and does not object to CSS’s recommendation to the DEA to decontrol naldemedine. (b) (4)

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

Not applicable.

9 Advisory Committee Meeting and Other External Consultations

Not applicable- an advisory committee meeting was not held for this application.

10 Labeling Recommendations

10.1. Prescribing Information

This section provides an outline of the important drug- and drug class-specific information to be included in the prescribing information (PI) for naldemedine, including a summary of the major points of discussion during the review process. Components of the PI that represent standard product labeling and did not raise concern by the review team are not referenced in this section.

Section 1: Indications and Usage

- The following treatment indication was proposed by the Applicant:

“SYMPROIC is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.”

The proposed indication reflects the patient population for which clinical trials were conducted to support this NDA. The proposed language is consistent with the indication approved for other PAMORAs with similar clinical trial programs. However, discussions were initiated during the time period of this application review to evaluate the adequacy of this indication to reflect the intended treatment population for whom this drug and other members of the PAMORA drug class has been determined to be safe and effective and consider class-wide changes to the stated indication in the PI for these drugs. Discussion was still ongoing at the time of

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submission of this review.

Section 2.1: Administration

- The Applicant's proposed PI included the following statement concerning opioid management when prescribing naldemedine (also included in the PI of other PAMORAs):

"Alteration of analgesic dosing regimen prior to initiating SYMPROIC is not required."

This statement is consistent with the PI for other PAMORAs approved for the same indication and is supported by the naldemedine clinical trial safety data. In the naldemedine safety population, there was a low incidence of reduced opioid efficacy and/or non-GI opioid withdrawal with naldemedine treatment, supporting that naldemedine may be safely initiated without alteration of the patient's opioid medication regimen. Although not a specific administration instruction, this statement has been included in Section 2.1 because it provides important safety-related patient management information aimed to prevent unnecessary opioid dosage increases.

- The Applicant proposed the following statement regarding minimum opioid usage in the naldemedine clinical trial population in the Administration section:

[REDACTED] (b) (4)

The rationale for referencing the opioid treatment history of the clinical trial population in the administration instructions of the PI is to inform providers of the possibility that patients with lower opioid exposures than the clinical trial population may experience lesser pharmacological effects with naldemedine treatment. This concern is based on clinical experience with opioid antagonists (i.e., naloxone) in which lower doses of these medications are needed to reverse the effects of opioids in highly tolerant patients vs. more opioid naïve patients (both central and peripheral). It is not known whether the lack of opioid tolerance observed in the GI tract (i.e., mechanism responsible for lack of improvement in OIC) would make the GI tract less susceptible to changes in opioid antagonist sensitivity, and the efficacy of the PAMORAs has not been evaluated in patients with subacute/acute opioid exposures. Therefore, the possibility of poor treatment response in these patients represents important contextual information for evaluation of OIC treatment options and assessment of treatment response in the clinical setting.

In the proposed naldemedine PI, the Applicant has omitted the statement that accompanies the proposed language [REDACTED] (b) (4)

[REDACTED] The review team acknowledged the Applicant's disagreement with the language of the omitted statement. However, the proposed PI [REDACTED] (b) (4)

(b) (4) Therefore, the review division has composed the following alternative language for consideration by the Applicant: "Patients receiving opioids for less than 4 weeks may not respond as well to SYMPROIC." Labeling negotiations were still ongoing at the submission of this review.

- The proposed PI includes a statement (b) (4)

This reviewer agrees that data from the long-term safety study provide adequate evidence to support the Applicant's position that naldemedine can be safely administered in patients receiving maintenance laxative treatment. In the long-term safety study, ~66% of subjects received concomitant treatment with maintenance laxatives. Although the rate of GI reactions during the long-term trial was higher during the first 12 weeks compared to the 2 replicate 12-week pivotal trials, these differences could not be attributed directly to concomitant laxative use and was not associated with any significant sequelae.

This recommendation (b) (4)

(b) (4) Therefore, the Agency recommended deletion of the proposed statement.

- Discontinue SYMPROIC if treatment with the opioid pain medication is also discontinued.

Treatment with naldemedine or other PAMORAs is only indicated in patients receiving opioid pain medications and should be promptly discontinued if opioid treatment is discontinued.

Section 2.2: Dosage

- The proposed dosage of naldemedine is 0.2 mg orally once daily

This dosage of naldemedine represents the dosing regimen evaluated in phase 3 clinical trials.

- The proposed PI states that naldemedine may be administered with or without food.

In phase 2/3 clinical trials, naldemedine was administered without regard to food. The Applicant conducted a phase 1 food-effect PK study, in which the AUC of naldemedine was unchanged following a high fat meal, though a decrease in C_{max} of 35% was observed. The fed state was also associated with a delay in T_{max} from 0.75 hours in the fasted state to 2.50 hours. No changes to medication administration were implemented based on these results, and the clinical pharmacology review team agreed that changes in dosing are not needed based on results of the food-effect study. The clinical pharmacology review concluded that the phase 2/3

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clinical trial data are adequate to support the proposed dosing regimen.

Section 3: Dosage forms and Strengths

An adequate description of the to-be-marketed product was provided in compliance with the PLR labeling guidelines.

Section 4: Contraindications

- Two clinical contraindications to naldemedine use were included in the proposed PI—(1) patients with suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction and (2) patients with serious or severe hypersensitivity reaction to naldemedine or any of its components.

This reviewer agrees with the proposed contraindications. Both represent class-wide safety concerns and are consistent with the other members of the PAMORA drug class. Of note, a single SAE of hypersensitivity (possible anaphylaxis), was reported during naldemedine clinical trials. (see Table 73). No additional information is recommended for this section based on the safety review for this product.

- The Applicant also proposed [REDACTED] (b) (4)

Although naldemedine has been identified as a CYP3A substrate, the Clinical Pharmacology review team did consider the increase in naldemedine exposure with these drugs (...) sufficient to warrant a contraindication to treatment. An information request was issued to the Applicant and consensus on this issue was reached during the review cycle. [REDACTED] (b) (4)

[REDACTED] Furthermore, no safety concerns were identified in naldemedine-treated patients who received moderate or severe CYP3A4 inhibitors during clinical trials.

Section 5: Warnings and precautions

- The Applicant included 2 warnings and precautions in the proposed PI—gastrointestinal perforation and opioid withdrawal.

The proposed warnings and precautions are considered appropriate and are consistent with the other members of the PAMORA drug class. These represent class-wide safety concerns and should be described in this section of the PI regardless of the incidence of these events in clinical trials. The naldemedine safety review did not identify any product-specific concerns; therefore, no additional information is recommended for this section.

Section 6: Adverse Reactions

- In this section of the proposed PI, the Applicant provided [REDACTED] (b) (4)

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(b) (4)

This reviewer disagrees (b) (4). Specifically, the use of laxatives, other than prescribed rescue treatment with Bisacodyl, was prohibited in Studies V9231 and V9232 (replicate 12-week trials), while Study V9235 (the long-term safety trial) permitted concomitant use of maintenance laxatives during study participation. (b) (4) the description and results of Study V9235 should be presented separately in the label to reflect this major difference in study procedures.

- Although the proposed PI included a subsection dedicated to opioid withdrawal (OW) adverse events, the structure and content were based on the Movantik PI.

The proposed OW information was not considered an adequate reflection of the naldemedine clinical trial data. Because the naldemedine program included more comprehensive procedures for defining and identifying cases of opioid withdrawal (OW), compared to other PAMORAs, including Movantik, global revisions to this section of the labeling were recommended, with extensive input from DAAAP, to more accurately reflect the nature and results of safety assessments conducted for this product. An information request was sent to the Applicant requesting (b) (4)

(b) (4)
(b) (4)
(b) (4) Based on the data provided by the Applicant, the Division has proposed the following summary for the Applicant's consideration:

"In Studies 1, 2 and 3 adverse events consistent with opioid withdrawal were based on investigator assessment and adjudicated based upon the occurrence of at least 3 adverse events potentially related to opioid withdrawal with onset of a constellation of those symptoms occurring on the same day or within one day of each other.

Adverse events of possible opioid withdrawal could include non-gastrointestinal (GI) symptoms (e.g., hyperhidrosis, hot flush or flushing, chills, tremor, tachycardia, anxiety, agitation, yawning, rhinorrhea, increased lacrimation, sneezing, feeling cold, and pyrexia), GI symptoms (e.g., vomiting, diarrhea, or abdominal pain), or both GI and non-GI symptoms.

In pooled Studies 1 and 2, the incidence of adverse reactions of opioid withdrawal was (b) (4)% (8/542) for SYMPROIC and (b) (4)% (3/546) for placebo. In Study 3 (52-week data), the incidence was (b) (4)% (20/621) for SYMPROIC and (b) (4)% (9/619) for placebo. Most SYMPROIC treated subjects experienced nearly equal incidence of GI only or both GI and non-GI symptoms."

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Relevant negotiations were ongoing at time of this review.

Section 7: Drug Interactions



Section 8

The structure and content of all Section 8 subsections containing information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential were revised in consultation with the Maternal Health Staff to comply with current PLLR regulatory requirements for all drugs. Additional detail is only provided for application-specific review issues raised during labeling discussions.

Section 8.1: Use in Pregnancy

- Naldemedine crosses the placenta, and may precipitate opioid withdrawal in a fetus due to the immature fetal blood brain barrier.

The safety of naldemedine has not been studied in pregnant women, although reports of PAMORA treatment during pregnancy are emerging in the medical literature. OW is a recognized risk associated with this drug class. Because naldemedine crosses the placenta, there is a potential for OW in a fetus when these medications are used in pregnant women, with concerns that the immature fetal blood-brain barrier increases the risks of OW in the fetus. This concern is reflected in the current PI for Movantik and Relistor. (“The use of MOVANTIK/RELISTOR during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood brain barrier”.)

Unlike OW in adults, there is no medically-defined term for “fetal opioid withdrawal.” Nevertheless, adverse consequences, including miscarriage, preterm birth, meconium passage, stillbirth and elevated epinephrine and norepinephrine levels have been reported with use of opioid antagonists, such as naloxone. Because these medications are typically used to rapidly reverse the effects of opioids in patients with respiratory depression, the applicability of these data to the PAMORA subclass of opioid antagonists may be limited. Nonclinical studies of naldemedine did not show any adverse effects on embryo-fetal development or postnatal development. However, these studies cannot be used to evaluate the risk of opioid withdrawal in a fetus with naldemedine treatment under expected clinical conditions because animals did not receive concurrent opioid treatment.

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Several issues were addressed to successfully convert pregnancy-related information into PLLR format.

Recommendations for interventions to minimize risk to the fetus should be evaluated by antenatal surveillance for signs of distress after SYMPROIC use until the fetus and mother are stabilized. When safe, alternative treatments are available, such is the case for OIC; use of medications with unclear risk of harm to the fetus is generally not advisable.

Based on discussions with DPMH, the recommended labeling language related to the theoretical risk of opioid withdrawal in both the developing fetus and the breastfed infant (see labeling discussion for section 8.2) was adjusted to advise the prescriber to consider risks and benefits for the pregnant woman, or the importance of the drug to a breastfeeding woman

Section 8.2: Lactation



(b) (4)

Based on discussions with DPMH, the labeling language was adjusted to address the theoretical risk of opioid withdrawal in both the developing fetus (See labeling discussion for Section 8.1) and the breastfed infant. The labeling language was adjusted to advise the prescriber to consider risks and benefits for the pregnant woman, or the importance of the drug to a breastfeeding woman. The labeling language recommends discontinuation of nursing or the drug due to the potential for serious adverse reactions, including opioid withdrawal in nursing infants. This decision should take into account the importance of the drug to the mother.

There is no information regarding the presence of naldemedine in human milk, the effects on the breastfed infant, or the effects on milk production. Naldemedine was present in the milk of rats [see Data]. Because of the potential for serious adverse reactions, including opioid withdrawal in breastfed infants, a decision should be made to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother. If drug is discontinued in order to minimize drug exposure to a breastfed infant, advise women that breastfeeding may be resumed 3 days after the final dose of SYMPROIC.

Section 8.4: Pediatric Use

Summary: This section includes the standard pediatric labeling for all drugs which have not been evaluated in children: “The safety and effectiveness of naldemedine have not been established in pediatric patients.” This reviewer notes that PREA studies for this product have been waived and the Applicant currently has no planned pediatric evaluations.

8.5: Geriatric Use

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Summary: In the judgment of the Clinical and Statistical reviewers, the subgroup of naldemedine-treated patients 65 years and older was deemed adequate to assess the safety or efficacy of naldemedine for this demographic group. The review team agrees with the Applicant's conclusion that subgroup analyses did not identify any overall differences in the safety or effectiveness of naldemedine between this population and younger individuals.

8.6 Hepatic Impairment

- The proposed PI recommends avoiding use of naldemedine in patients with severe hepatic impairment, and no dosage adjustment is recommended for patients with mild or moderate hepatic impairment.

Dosing recommendations for patients with hepatic impairment have been reviewed by the Clinical Pharmacology team. The Clinical Pharmacology reviewers agree data from the drug development program support the proposed dosing recommendations.

Section 10: Overdosage

The Applicant has included data from phase 1 single and multiple ascending dose studies in healthy individuals treated with doses up to 150 times, as well as single and multiple ascending dose trials in patients with OIC, using doses up to 15 and 2 times the recommended dose, respectively. In both populations, dose-dependent increases in gastrointestinal-related adverse reactions, including abdominal pain, diarrhea, and nausea, were observed. In patients with OIC, non-GI symptoms of chills, hyperhidrosis, and dizziness were also reported.

- No antidote for naldemedine is known. Hemodialysis is not an effective means to remove naldemedine from the blood.

Section 11: Description

This section includes the required information, including active ingredient, chemical names, structural formula, empirical formula, molecular weight, and list of excipients in compliance with approved PLR format.

12.1 Mechanism of Action

Naldemedine is an opioid antagonist with binding affinities for mu-, delta-, and kappa-opioid receptors. Naldemedine functions as a peripherally-acting mu-opioid receptor antagonist in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids.

Naldemedine is a derivative of naltrexone to which a side chain has been added that increases the molecular weight and the polar surface area, thereby reducing its ability to cross the blood-brain barrier (BBB); the CNS penetration of naldemedine is expected to be negligible at the recommended dose. (b) (4), naldemedine is a substrate of the P-glycoprotein (P-gp) efflux transporter, (b) (4).

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(b) (4)

No changes were recommended to the content of this section. Minor revisions were recommended to decrease the promotional nature

12.2 Pharmacodynamics

The Clinical Pharmacology information was reviewed in detail by the Clinical Pharmacology Reviewer. The Clinical Pharmacology reviewer agreed that the PK data were similar in individuals with various degrees of renal impairment, including ESRD as presented in Section 12 of the proposed PI. Because the dosage of naldemedine does not need to be adjusted based on renal function, (b) (4)

13 NONCLINICAL TOXICOLOGY

This section of the label was reviewed in detail by the nonclinical reviewers. For a detailed explanation of recommended changes to this section of the label, the reader is referred to the full nonclinical review for discussion of recommended minor edits.

14 Clinical Studies

- Inclusion of actual/numerical efficacy data only from the two replicate, 12-week, randomized, double-blind, placebo-controlled trials in which SYMPROIC was used without laxatives in patients with OIC and chronic non-cancer pain. For Study V9235, efficacy was not a primary endpoint. and the study design with respect to efficacy assessments and concurrent laxative treatment were neither prespecified nor sufficiently
- The label should reflect that the assessment of efficacy was based

16: How Supplied/Storage and Handling

SYMPROIC is supplied as 0.2 mg naldemedine tablets in a bottle of 90 tablets - NDC 59630-222-90.

Store SYMPROIC in light resistant container at 20-25°C (68 to 77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature

10.2. Patient Labeling

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Administration

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Advise patients to discontinue SYMPROIC if treatment with the opioid pain medication is also discontinued.

Gastrointestinal Perforation

Advise patients to discontinue SYMPROIC and to promptly seek medical attention if they develop unusually severe, persistent or worsening abdominal pain [*see Warnings and Precautions (5.1)*].

Opioid Withdrawal

Advise patients that clusters of symptoms consistent with opioid withdrawal may occur while taking SYMPROIC and to contact their healthcare provider if these symptoms occur [*see Warnings and Precautions (5.2)*].

Pregnancy

Advise females of reproductive potential, who become pregnant or are planning to become pregnant, that the use of SYMPROIC during pregnancy may precipitate opioid withdrawal in a fetus due to the undeveloped blood-brain barrier [*see Use in Specific Populations (8.1)*].

Lactation

Advise women that breastfeeding is not recommended during treatment with SYMPROIC and for 3 days after the final dose [*see Use in Specific Populations (8.2)*].

10.3. **Nonprescription Labeling**

Not applicable

11 Risk Evaluation and Mitigation Strategies (REMS)

The review team determined that a REMS was not needed for this product.

11.1. **Safety Issue(s) that Warrant Consideration of a REMS**

Not applicable

11.2. **Conditions of Use to Address Safety Issue(s)**

Not applicable

11.3. **Recommendations on REMS**

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Not applicable

12 Postmarketing Requirements and Commitments

A postmarketing requirement for an epidemiological study is planned to further assess the risk of MACE with naldemedine treatment. As is commonly the case with rare events, the premarketing safety database was not sufficient to establish whether this agent is associated with an unacceptable risk of MACE with naldemedine, i.e., greater than 1.8-2-fold increase risk for drug to treat a non-lethal condition for which there is not a substantial unmet need for treatment options. The naldemedine clinical trial data did not reveal a safety signal for MACE as seen with alvimopan, thus supporting the marketing approval of this drug for OIC without the need for a REMS. However, there is plausible mechanism to substantiate the safety signal observed during naldemedine clinical trials, which could also explain why other members of the PAMORA drug class have lesser risk. At this time, PMR studies under FDAAA are ongoing for other PAMORAs; therefore, this safety concern remains unresolved.

An assessment was conducted by the Office of Surveillance and Epidemiology (OSE) to determine whether the Agency's Active Risk Identification and Analysis (ARIA) system would be sufficient for post-marketing surveillance for MACE, in lieu of a PMR study conducted by the Applicant. Because this system may not fully capture out-of-hospital deaths and concurrent conditions/risk factors not explicitly recorded in hospital records, it was concluded that a PMR under FDAAA is necessary to obtain adequate, interpretable post-marketing data to address this specific safety concern.

13 Appendices

13.1. References

1. Panchal SJ, Müller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. *International Journal of Clinical Practice*. 2007;61(7):1181-1187. doi:10.1111/j.1742-1241.2007.01415.x.
2. McNicol E Horowicz-Mehler N Fisk RA et al Management of opioid side effects in cancer-related and chronic noncancer pain: A systematic review. *J Pain* 2003;4:231-56
3. Bell TJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). *Pain Med*. 2009;10(1):35-42 80%

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4. Kalso E, Edwards JE, Moore A, et al. Opioids in chronic non cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112:372–80.
5. Leppert W. The impact of opioid analgesics on the gastrointestinal tract function and the current management possibilities. *Contemporary Oncology*. 2012;16(2):125-131. doi:10.5114/wo.2012.28792.
6. Dorn S, Lembo, Cremonini F. Opioid-induced bowel dysfunction: epidemiology, pathophysiology, diagnosis, and initial therapeutic approach. *Am J Gastroenterol Suppl* 2014; 2:31–37.
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http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208271s000lbl.pdf
8. Movantik Label (label approval date
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9. NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, Plaut M, Cooper SF, Fenton MJ, Arshad SH, Bahna SL, Beck LA, Byrd-Bredbenner C, Camargo CA Jr, Eichenfield L, Furuta GT, Hanifin JM, Jones C, Kraft M, Levy BD, Lieberman P, Luccioli S, McCall KM, Schneider LC, Simon RA, Simons FE, Teach SJ, Yawn BP, Schwaninger JM. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010 Dec;126(6 Suppl):S1-58.
10. Food and Drug Administration, Anesthetic and Analgesic Drug Product Advisory Committee, Transcript, Wednesday, June 11, 2014, page 49-80.
11. ICH Harmonised Tripartite Guideline- The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions (E1)
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1/Step4/E1_Guideline.pdf

13.2. Financial Disclosure

None of the investigators in any of the 3 phase 3 clinical trials (Studies V9231, 9232, and 9235) had reportable financial information to disclose. The following tables include more detailed financial disclosure information for each of the 3 trials.

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 Lauren Weintraub, Clinical Reviewer
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1. Covered Clinical Study: 1314V9231

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 68 principal investigators, 141 sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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2. Covered Clinical Study: 1315V9232

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 69 principal investigators, 232 sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Clinical Review
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3. Covered Clinical Study: 1326V9235

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 195 principal investigators, 733 sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Supplemental Tables and Figures

13.3.1. Tabular Listing of All Naldemedine Clinical Trials

Table 83: Listing of all Naldemedine Clinical Trials (Submitted by Applicant, NDA 208854, Module 5.2)

Table 1 Listing of Clinical Studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Number of Subjects Dosed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.1.1 Phase 1 BA and Food effect, PK	0909V9212	Comparative bioavailability of 10 mg tablet and food effect study in healthy Japanese subjects	Open-label, randomized, three-period crossover study	Naldemedine 10 mg, Oral, Solution, fasted	15	Healthy subjects	3 non-consecutive days	Complete; Full
				Naldemedine 10 mg, Oral, Tablets, fasted				
				Naldemedine, Oral, Tablets, fed				
5.3.1.2 Phase 1 BA/FE for to-be-marketed formulation, PK	1311V921A	To evaluate the relative bioavailability and food effect of the to-be-marketed tablet formulation of naldemedine in healthy subjects	Open-label, randomized, three-period crossover study	Naldemedine 0.2 mg (2 x 0.1 mg), fasted	18	Healthy adult subjects	3 non-consecutive days	Complete; Full
				Naldemedine 1 x 0.2 mg, fasted				
				Naldemedine 1 x 0.2 mg, fed, Oral				
5.3.3.1 Phase 1 Dose escalation, PK	0824V9211	To evaluate the safety, tolerability, and pharmacokinetics of a single oral dose of naldemedine in healthy Japanese adult male subjects	Single-dose, randomized, double-blind, dose-escalation study	Naldemedine 0.1, 0.3, 1, 3, 10, 30 mg or placebo, Single dose, Oral, Solution	56; naldemedine 42, placebo 14	Healthy Japanese adult male subjects	One day (Single dose administration)	Complete; Full
				Naldemedine 100 mg or placebo, Single dose, Oral, Suspension				

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Number of Subjects Dosed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.3.1 Phase 1 Dose escalation, PK	0917V9213	To evaluate the safety, tolerability, and pharmacokinetics of multiple oral doses of naldemedine in healthy Japanese adult males	Double-blind, randomized, placebo-controlled study	Naldemedine 3, 10, 30 mg, placebo, Once daily administration x 10 days, Oral	36; naldemedine 27, placebo 9	Healthy Japanese adult male subjects	10 days	Complete; Full
				Naldemedine 3 and 10 mg tablets				
				Matching placebo				
5.3.3.1 Phase 1 Mass balance, PK	1016V9215	To assess the mass balance of naldemedine in healthy subjects To characterize the metabolism and routes of elimination for naldemedine and naldemedine metabolites	Open-label, non-randomized, absorption, metabolism, and excretion study	Oxadiazole- ¹⁴ C]-naldemedine 2 mg, Single dose, Oral Solution	12 total; 6 per group	Healthy adult male subjects	One day (Single dose administration)	Complete; Full
				[Carbonyl- ¹⁴ C]-naldemedine 2 mg, Single dose, Oral Solution				

Table 83 (cont.): Listing of all Naldemedine Clinical Trials

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Number of Subjects Dosed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.3.3 Phase 1 Intrinsic Factor PK (Renal impairment)	1401V921B	To evaluate the effect of impaired renal function on naldemedine pharmacokinetics	Open-label, non-randomized study	Naldemedine 0.2 mg tablet, Single dose	41; 9 subjects with mild, 9 moderate renal impairment and 8 ESRD requiring dialysis 6 subjects with severe renal impairment 9 healthy subjects	Subjects with mild, moderate, severe renal impairment and ESRD requiring hemodialysis Healthy (gender, age, BMI)-matched control subjects (matched to subjects with moderate renal impairment)	Mild, moderate or severe renal impairment: One day ESRD requiring hemodialysis: 2 non-consecutive days	Complete; Full
				Naldemedine 0.2 mg, Oral				
5.3.3.3 Phase 1 Intrinsic Factor PK (Hepatic impairment)	1402V921C	To evaluate the effect of impaired hepatic function on naldemedine pharmacokinetics	Open-label, non-randomized study	Naldemedine 0.2 mg tablet, Single dose	24; 8 subjects per cohort	Subjects with mild or moderate hepatic impairment Healthy (gender, age and BMI)-matched control subjects (matched to subjects with mild hepatic impairment)	One day (Single dose administration)	Complete; Full
				Naldemedine 0.2 mg, Oral				
5.3.3.4 Phase 1 Extrinsic Factor PK (DDI)	1202V9218	To determine the effect of a single dose of cyclosporine on naldemedine pharmacokinetics	Open-label, randomized, 2-period crossover study	Naldemedine 0.4 mg, Single dose, Oral, Tablet (0.1 mg) Cyclosporine 600 mg, Single dose, Oral Solution	14	Healthy adult male subjects	Two non-consecutive days	Complete; Full

Table 83 (cont.): Listing of all Naldemedine Clinical Trials

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Number of Subjects Dosed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.3.4 Phase 1 Extrinsic Factor PK (DDI)	1403V921D	To evaluate the effect of repeated administration of rifampin 600 mg on the pharmacokinetics of a single dose of naldemedine 0.2 mg compared with a single dose of naldemedine 0.2 mg administered alone, in healthy adult subjects	Open-label, one-sequence, two-period, crossover, drug-drug interaction study	Naldemedine 0.2 mg, Single dose, Oral, Tablet (0.2 g) Rifampin 600 mg, Daily administration x 17 days, Oral Capsule (300 mg)	14	Healthy male and female subjects	Two non-consecutive days of single doses of naldemedine and 17 consecutive days of rifampin	Complete; Full

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Number of Subjects Dosed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.3.4 Phase 1 Extrinsic Factor PK (DDI)	1502V921E	To evaluate the effect of repeated administration of itraconazole 200 mg or fluconazole 200 mg on the pharmacokinetics of a single dose of naldemedine 0.2 mg compared to a single dose of naldemedine 0.2 mg administered alone, in Japanese healthy adult subjects	Open-label, one-sequence, two period, crossover, drug-drug interaction Study	Naldemedine 0.2 mg, Single dose, Oral, Tablet (0.2 mg) Itraconazole, Solution (Itrazole® Oral Solution 1%) Itraconazole 200 mg (20 mL) BID x 1 day, QD x 5 days Fluconazole, Capsule (100 mg) Fluconazole 400 mg x 1 day, 200 mg x 5 days, Oral	28 total (itraconazole, 14; fluconazole, 14)	Healthy Japanese adult (male and female) subjects	Two non-consecutive days of single doses of naldemedine and 4 consecutive days of itraconazole or fluconazole	Complete; Full
5.3.4.1 Phase 1 PK	1101V9216	To evaluate the efficacy of a single oral dose of naldemedine for the reduction of opioid-induced nausea	Randomized, double-blind, placebo-controlled, parallel-group	Naldemedine 0.1, 1, 10 mg, placebo, Single doses, Oral Naldemedine 0.1, 1, 10 mg tablets Matching placebo	80 total (naldemedine 60, placebo 20)	Healthy adult subjects	One day (Single dose administration)	Complete; Full

Table 83 (cont.): Listing of all Naldemedine Clinical Trials

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Number of Subjects Dosed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.4.1 Phase 1 PK/PD (TQTc)	1204V9219	To evaluate the effect of naldemedine on the QT interval	Randomized, double-blind, placebo- and positive-controlled, 4-period, crossover study	Naldemedine 0.2, 1 mg, Single dose, Tablet (0.2 mg), Oral Moxifloxacin 400 mg, Single dose, Oral Tablet (400 mg) Matching placebo to naldemedine	56 naldemedine 0.2 mg 51, 1 mg 48, placebo QT/QTc evaluated 55, PK/QTc evaluated 53	Healthy male and female subjects	4 non-consecutive days of single doses	Complete; Full
5.3.5.1 Phase 2a Ascending - dose PK	1007V9214	To evaluate the safety and efficacy of single ascending doses of oral naldemedine in subjects physically dependent on opioids	Randomized, double-blind, placebo-controlled, single-ascending dose study	Naldemedine 0.01 and 0.03 mg, Oral solution, Oral Naldemedine 0.1, 0.3, 1, 3 mg Naldemedine 0.1 mg and 1 mg tablets, Oral Matching placebo tablets and oral solution	72 total; naldemedine: 0.01 mg: 9, 0.03 mg: 9, 0.1 mg: 9, 0.3 mg: 9, 1 mg: 9, 3 mg: 9 Placebo: 18	Patients with chronic non-cancer pain, OBD, and opioid physical dependence	One day (Single dose administration)	Complete; Full
5.3.5.1 Phase 2b Efficacy (Controlled Clinical Studies Pertinent to the Claimed Indication)	1107V9221	To evaluate the efficacy and safety of naldemedine for the treatment of OIC in patients with chronic non-cancer pain	Randomized, double-blind, placebo-controlled, parallel-group study	Naldemedine 0.1 and 0.2 mg, tablets Naldemedine 0.1, 0.2 and 0.4 mg, QD, Oral Matching placebo	244 naldemedine: 0.1 mg: 61, 0.2 mg: 60, 0.4 mg: 61 Placebo: 61	Patients with chronic non-cancer pain and OIC	28 days	Complete; Full
5.3.5.1 Phase 3	1314V9231	To evaluate the efficacy and safety of naldemedine for the treatment of OIC in patients with chronic non-cancer pain	Randomized, double-blind, placebo-controlled, parallel-group study	Naldemedine 0.2 mg, tablets Naldemedine 0.2 mg, QD, Oral Matching placebo	543 naldemedine 0.2 mg: 271 Placebo: 272	Patients with chronic non-cancer pain and OIC	12 weeks	Complete; Full
5.3.5.1 Phase 3	1315V9232	To evaluate the efficacy and safety of naldemedine for the treatment of OIC in patients with chronic non-cancer pain	Randomized, double-blind, placebo-controlled, parallel-group study	Naldemedine 0.2 mg, tablets Naldemedine 0.2 mg, QD; Oral Matching placebo	545 naldemedine 0.2 mg: 271 Placebo: 274	Patients with chronic non-cancer pain and OIC	12 weeks	Complete; Full
5.3.5.1 Phase 3	1326V9235	To evaluate the long-term safety of naldemedine for the treatment of OIC in patients with chronic non-cancer pain	Randomized, double-blind, placebo-controlled, parallel-group study	Naldemedine 0.2 mg, tablets Naldemedine 0.2 mg, QD, Oral Matching placebo	1240 naldemedine 0.2 mg: 621 Placebo: 619	Patients with chronic non-cancer pain and OIC	52 weeks	Core Data Set Complete; Full

Table 83 (cont.): Listing of all Naldemedine Clinical Trials

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Number of Subjects Dosed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.5.1 Phase 3	1336V9238	To evaluate the long-term safety study of naldemedine in Japanese subjects with chronic non-cancer pain	Open-label study	Naldemedine 0.2 mg, tablets	43 Naldemedine 0.2 mg: 43	Patients with chronic non-cancer pain and OIC	48 weeks	ongoing
				Naldemedine 0.2 mg, QD, Oral				
5.3.5.1 Phase 3	1339V9239	To evaluate the long-term safety study of naldemedine in Japanese subjects with chronic non-cancer pain receiving S 8117 (oxycodone hydrochloride hydrate)	Open-label study	Naldemedine 0.2 mg tablets, S-8117, Oral, tablets	10 Naldemedine 0.2 mg: 10	Patients with chronic non-cancer pain and OIC	48 weeks	ongoing
				Naldemedine 0.2 mg, QD, Oral				
				S-8117, QD, Oral				
5.3.5.4 Phase 2b	1108V9222	To evaluate the efficacy and safety of naldemedine for the treatment of OIC in cancer patients	Randomized, double-blind, placebo-controlled, parallel-group study	Naldemedine 0.1 mg and 0.2 mg, tablets	226 naldemedine 0.1 mg: 56 0.2 mg: 58 0.4 mg: 56 Placebo: 56	Patients with cancer and OIC	14 days	Complete; Full
				Naldemedine, 0.1 mg, 0.2 mg and 0.4 mg QD, Oral				
				Matching placebo				
5.3.5.4 Phase 3	1331V9236	To evaluate the efficacy and safety of naldemedine for the treatment of OIC in Japanese cancer patients	Randomized, double-blind, placebo-controlled, parallel-group study	Naldemedine 0.2 mg, tablets	193 Naldemedine 0.2 mg: 97 Placebo: 96	Patients with cancer and OIC	14 days	Complete; Full
				Naldemedine 0.2 mg, QD, Oral				
				Matching placebo				

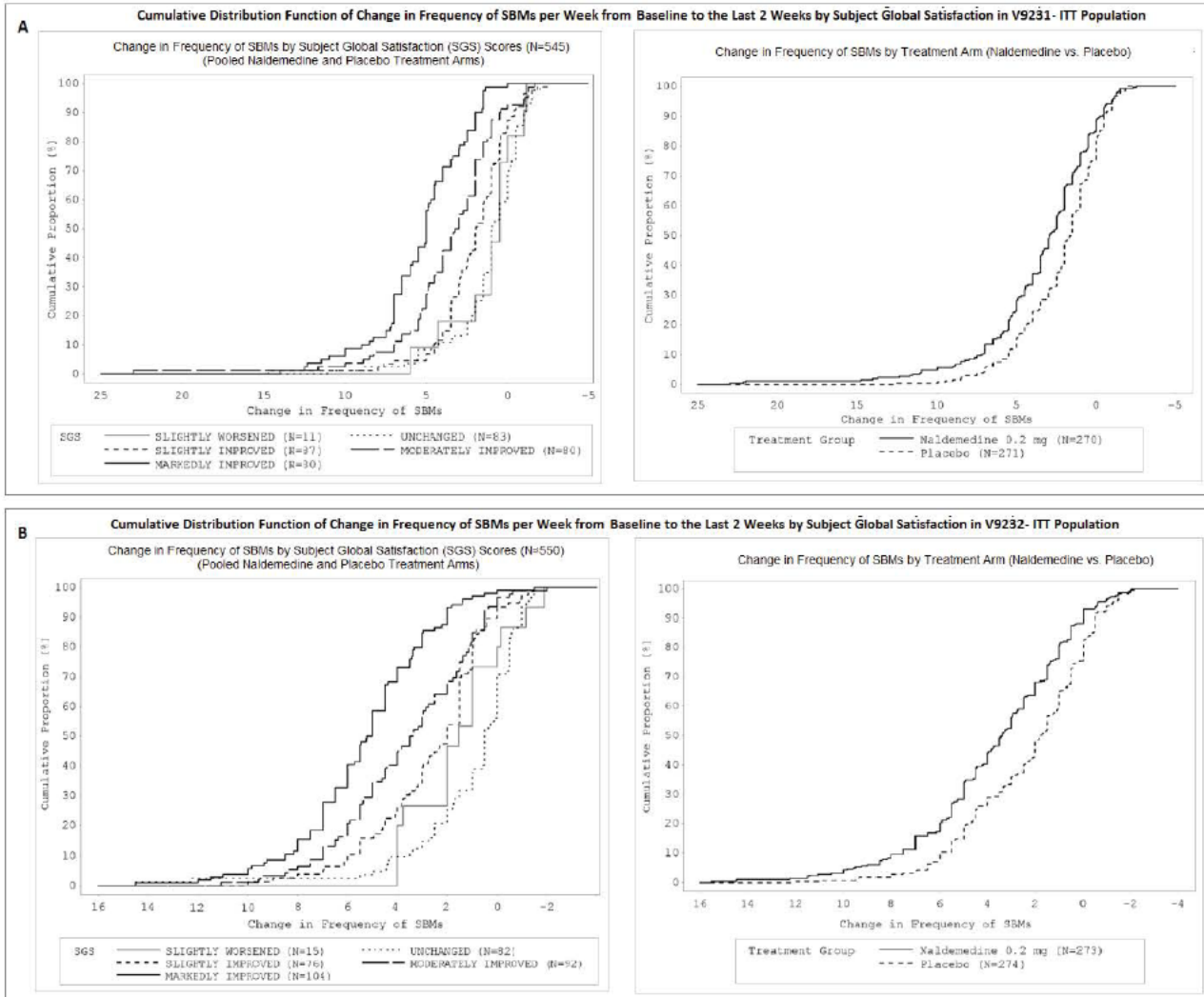
Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Number of Subjects Dosed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.5.4 Phase 3	1332V9237	To evaluate the long-term safety of naldemedine in cancer patients with OIC	Open-label study	Naldemedine 0.2 mg, tablets	131 Naldemedine 0.2 mg: 131	Patients with cancer and OIC	12 weeks	Complete; Full
				Naldemedine 0.2 mg, QD, Oral				

PK= pharmacokinetics; BA= bioavailability; FE= food effect; PD= pharmacodynamics; QTc= thorough QTc; OIC = opioid-induced constipation; ESRD = end stage renal disease; BMI = body mass index; DDI= drug-drug interaction.

13.3.2. Cumulative Distribution Frequency (CDF) Plots for Secondary Endpoints

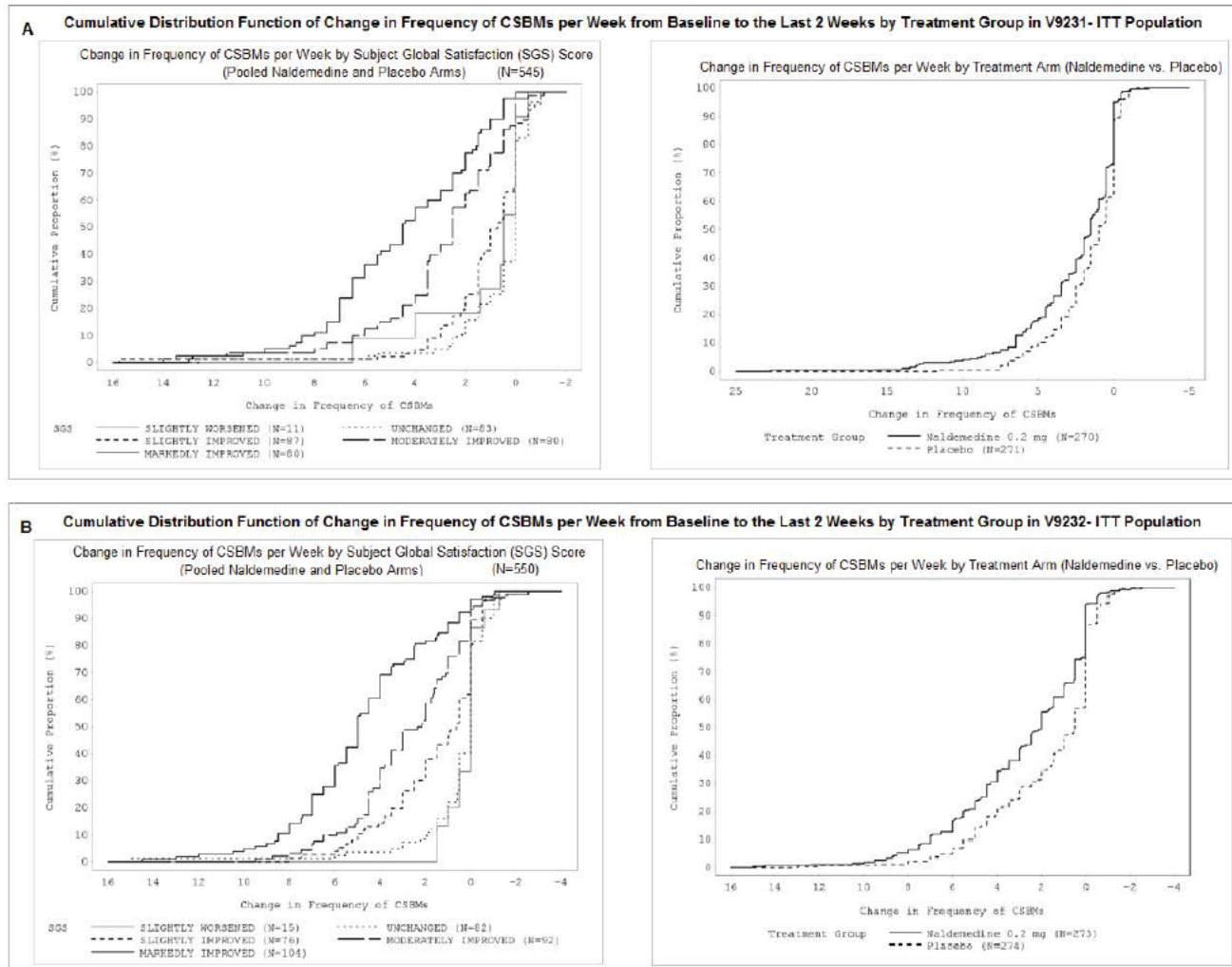
The following are the 12 groups of CDF plots of secondary endpoints data vs. SGS scores. Sets of 2 related plots—CDF plot of change in weekly frequency of specified BM event from baseline to the last 2 weeks of treatment (pooled naldemedine and placebo data) by SGS score with the corresponding CDF plot of change in frequency of specified BM events by treatment arm. (only SGS data at week 12. Therefore, these analyses were not done for the secondary endpoint of weekly SBM frequency from baseline to week 1 not done because no corresponding SGS data)

Figure 38: Cumulative Distribution Function of Change in Frequency of SBM per Week from Baseline to the Last 2 Weeks of the Treatment Period by Subject Global Satisfaction for Studies V9231 and V9232, Adjusted Data



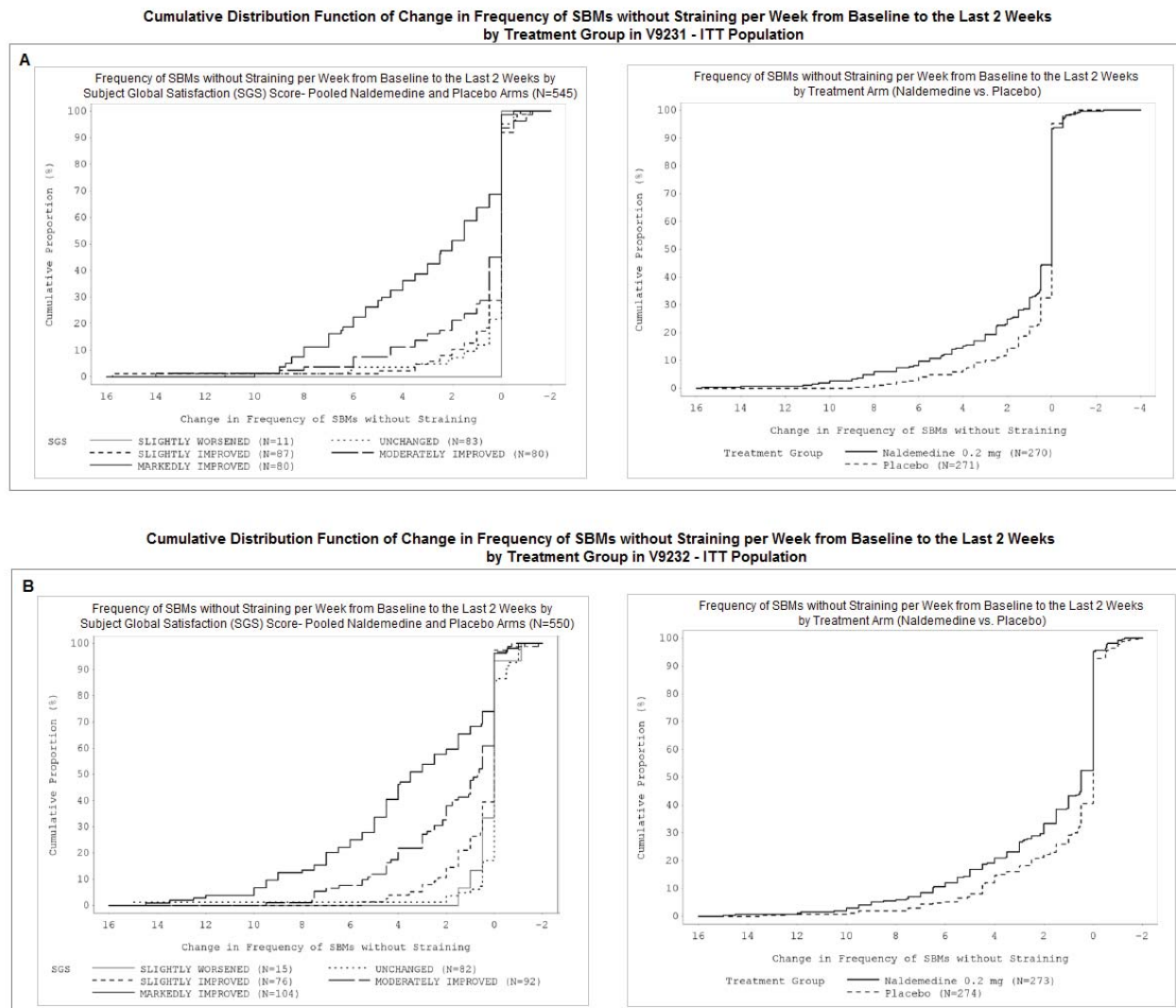
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Figure 39: Cumulative Distribution Function of Change in Frequency of CSBM per Week from Baseline to the Last 2 Weeks of the Treatment Period by Subject Global Satisfaction for Studies V9231 and V9232, Adjusted Data



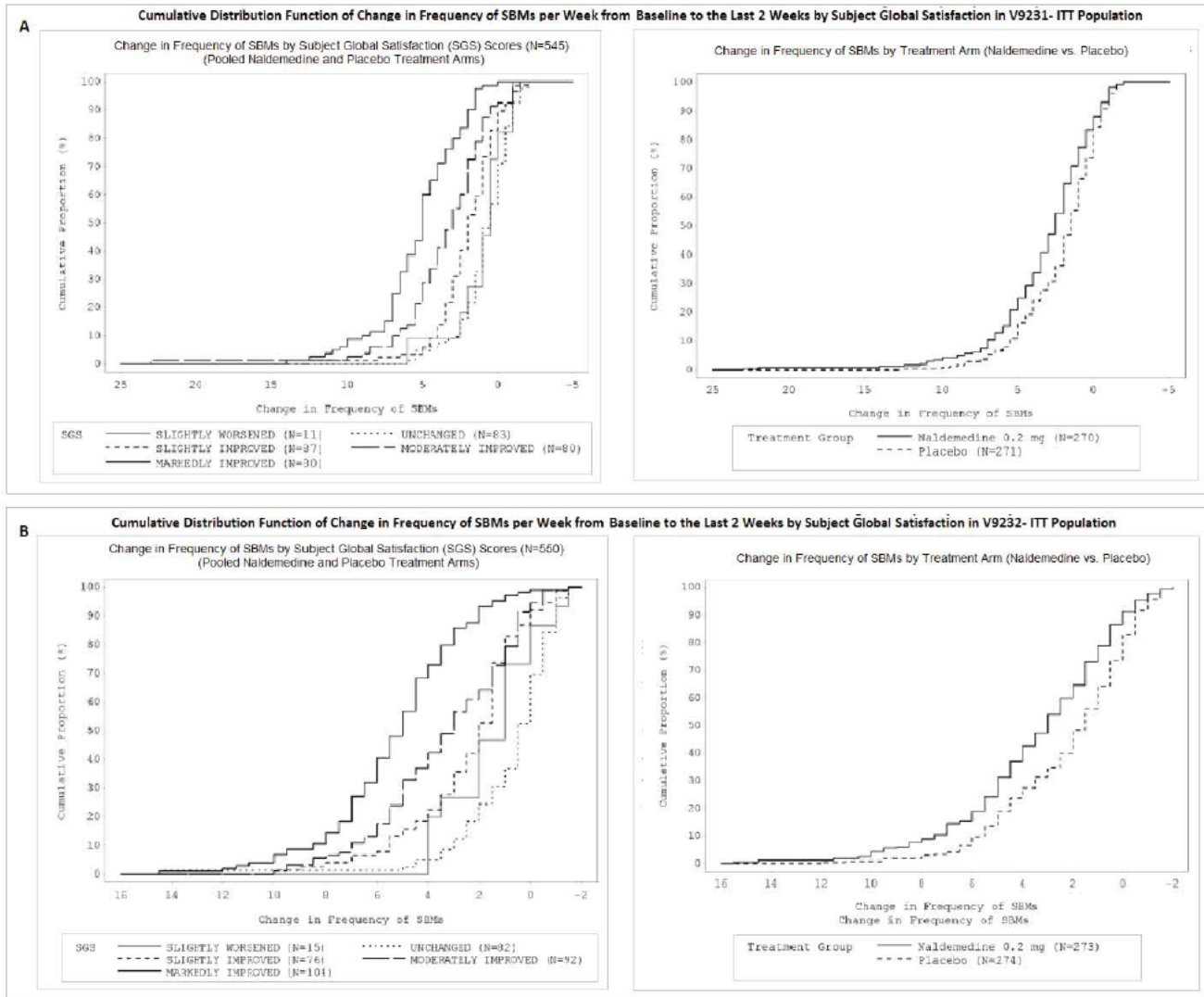
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Figure 40: Cumulative Distribution Function of Change in Frequency of SBM Without Straining per Week from Baseline to the Last 2 Weeks of the Treatment Period by Subject Global Satisfaction for Studies V9231 and V9232, Adjusted Data



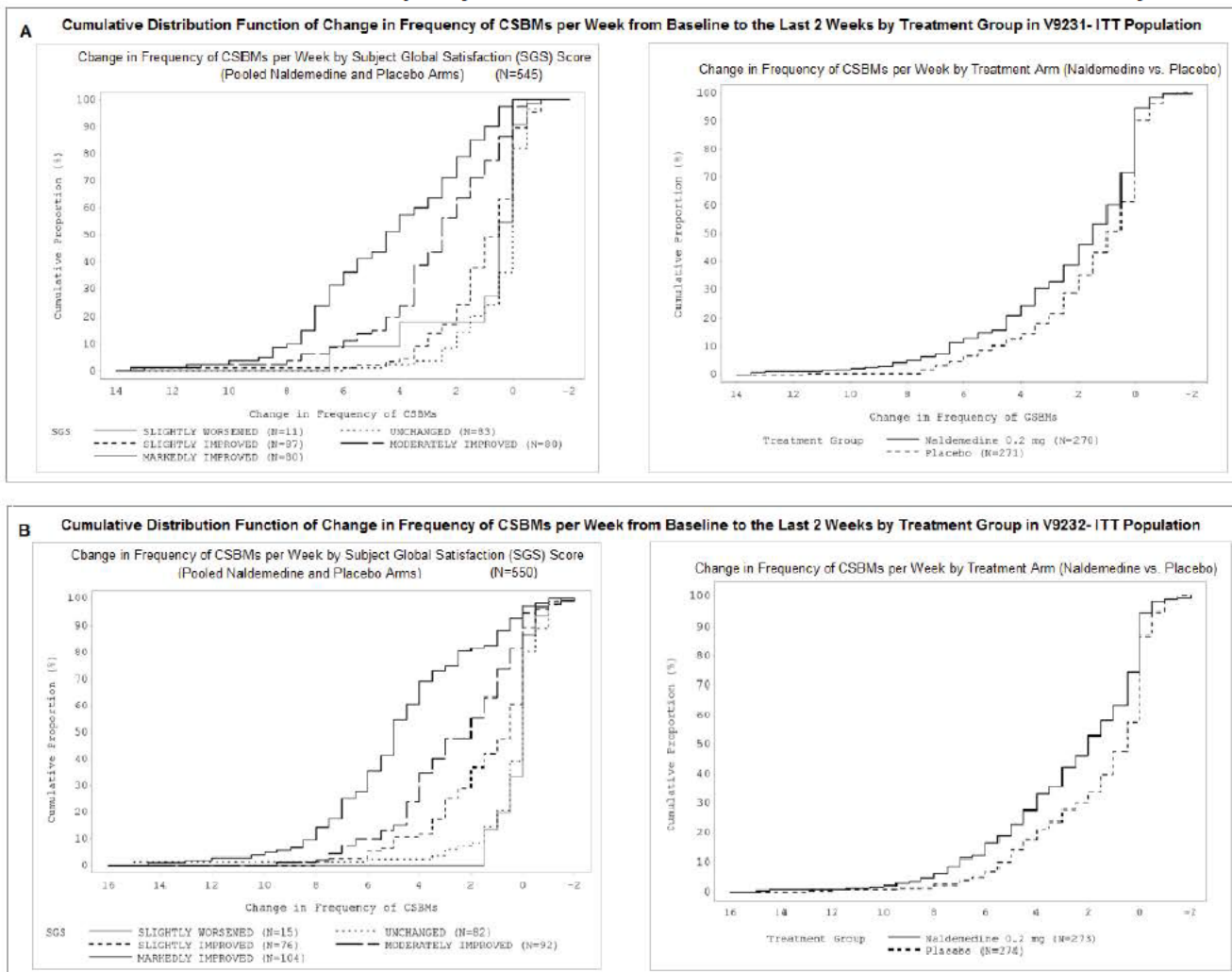
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Figure 41: Cumulative Distribution Function of Change in Frequency of SBM per Week from Baseline to the Last 2 Weeks of the Treatment Period by Subject Global Satisfaction for Studies V9231 and V9232, Unadjusted Data



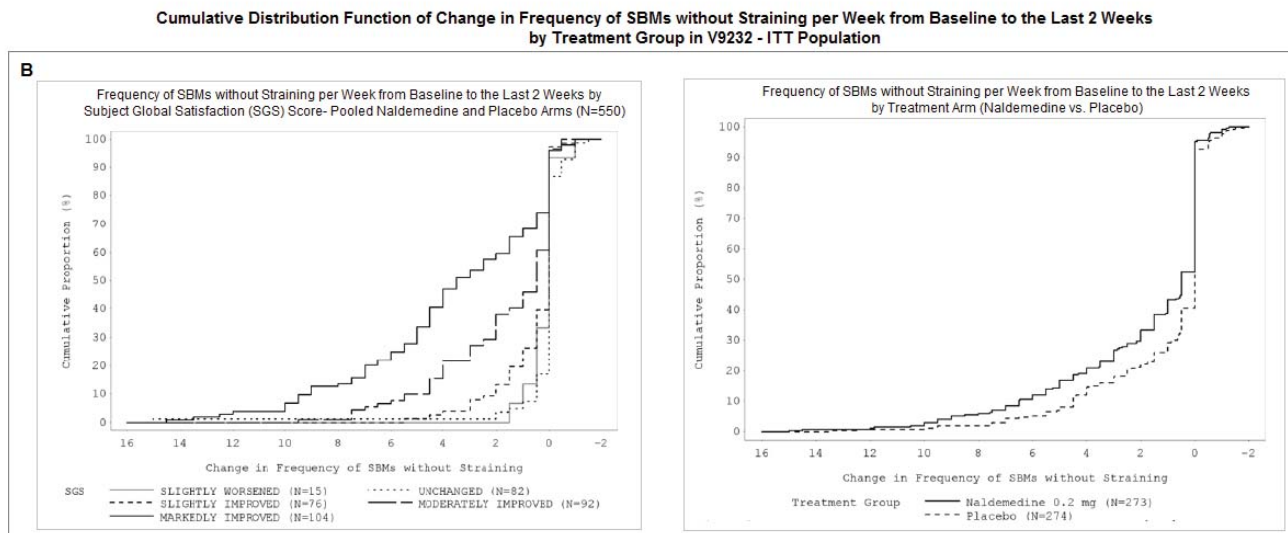
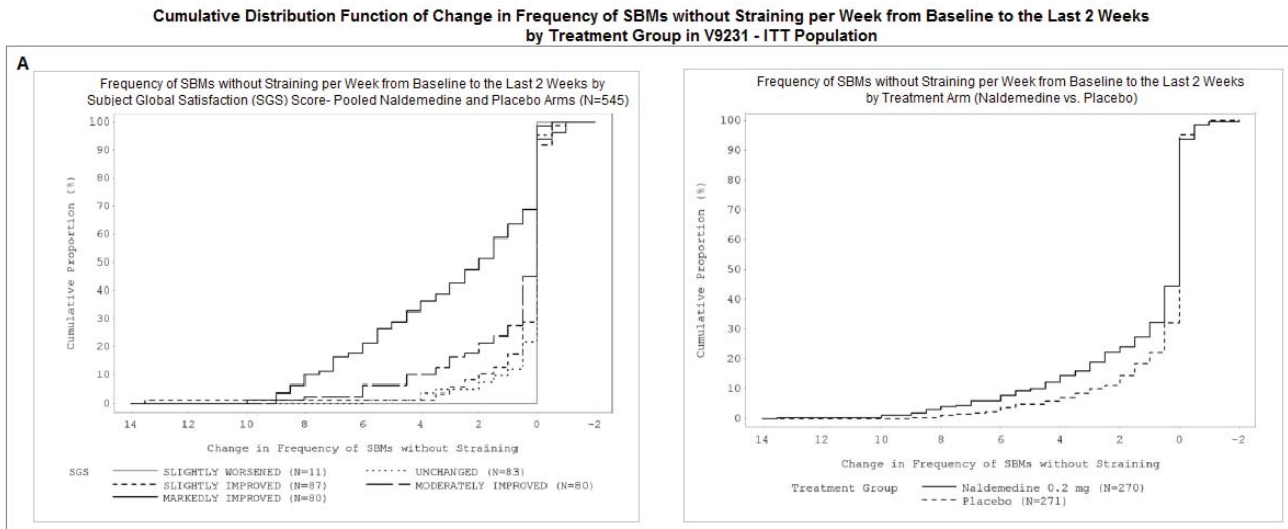
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Figure 42: Cumulative Distribution Function of Change in Frequency of CSBM per Week from Baseline to the Last 2 Weeks of the Treatment Period by Subject Global Satisfaction for Studies V9231 and V9232, Unadjusted Data



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Figure 43: Cumulative Distribution Function of Change in Frequency of SBM Without Straining per Week from Baseline to the Last 2 Weeks of the Treatment Period by Subject Global Satisfaction for Studies V9231 and V9232, Unadjusted Data



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/s/

LAUREN A WEINTRAUB
03/23/2017

ANIL K RAJPAL
03/23/2017