Report on the Deliberation Results

February 17, 2017
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Symproic Tablets 0.2 mg
Non-proprietary Name	Naldemedine Tosilate (JAN*)
Applicant	Shionogi & Co., Ltd.
Date of Application	March 30, 2016

Results of Deliberation

In its meeting held on February 9, 2017, the First Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product, and the re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

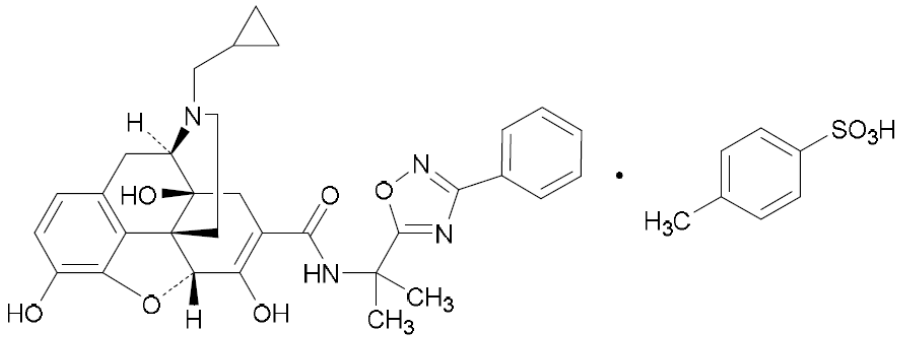
Review Report

January 18, 2017
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency.

Brand Name	Symproic Tablets 0.2 mg
Non-proprietary Name	Naldemedine Tosilate
Applicant	Shionogi & Co., Ltd.
Date of Application	March 30, 2016
Dosage Form/Strength	Each tablet contains 0.2 mg naldemedine (as naldemedine tosilate).
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{32}H_{34}N_4O_6 \cdot C_7H_8O_3S$

Molecular weight: 742.84

Chemical name:

(5R)-17-(cyclopropylmethyl)-6,7-didehydro-4,5-epoxy-3,6,14-trihydroxy-N-[2-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]morphinan-7-carboxamide mono(4-methylbenzenesulfonate)

Items Warranting Special Mention	None
Reviewing Office	Office of New Drug I

Results of Review

The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the data submitted demonstrate the efficacy of the product in the treatment of opioid-induced constipation and acceptable safety in view of the benefits indicated by the data submitted, as shown in Attachment.

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition.

Indication

Opioid-induced constipation

Dosage and Administration

The usual adult dosage is 0.2 mg of naldemedine administered orally once daily.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

November 30, 2016

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval

Brand Name	Symproic Tablets 0.2 mg
Non-proprietary Name	Naldemedine Tosilate
Applicant	Shionogi & Co., Ltd.
Date of Application	March 30, 2016
Dosage Form/Strength	Each tablet contains 0.2 mg naldemedine (as naldemedine tosilate).
Proposed Indication	Opioid-induced constipation

Proposed Dosage and Administration

The usual adult dosage is 0.2 mg of naldemedine administered orally once daily.

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List of Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve
$AUC_{0\text{-}24h}$	Area under concentration-time curve up to 24 hours
$AUC_{0\text{-}\tau}$	Area under concentration-time curve during dose interval
$AUC_{0\text{-}inf}$	Area under concentration-time curve up to infinity
BA	Bioavailability

BCRP	Breast cancer resistance protein
BPI	Brief pain inventory
Impurity A	[redacted]
BSS	Bristol stool form scale
CMA	Critical material attribute
C_{max}	Maximum plasma concentration
COWS	Clinical Opioid Withdrawal Scale
CPK	Creatine phosphokinase
CPP	Critical process parameter
CQA	Critical quality attribute
CSBM	Complete spontaneous bowel movement
CYP	Cytochrome P450
DAMGO	[D-Ala^2, N-Me-Phe^4, Gly^5-ol]-enkephalin
Impurity B	[redacted]
ED_{50}	50% effective dose
FAS	Full analysis set
Feu	Fraction of dose excreted into the urine
FOB	Functional observational battery
GC	Gas chromatography
GGT	Gamma-glutamyl transferase
Guidance for proper use of medical narcotics	Guidance for proper use of medical narcotics Guidance for use and management of medical narcotics in the treatment of cancer pain (Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, MHLW, March 2012)
Guideline for prescribing opioid analgesics for chronic non-cancer pain	Guideline for prescribing opioid analgesics for chronic non-cancer pain (Japan Society of Pain Clinicians, Working group for developing guideline for prescribing opioid analgesics for chronic non-cancer pain ed. July 2012)
Guideline on drug therapy for cancer pain, 2014	Guideline on drug therapy for cancer pain, 2014 (Specified Non-profit Corporation, Japanese Society for Palliative Medicine, Committee on Palliative Medicine Guidelines ed. May 2014)
hERG	Human ether-à-go-go related gene
HPLC	High performance liquid chromatography
ICH	International conference on harmonization of technical requirements for registration of pharmaceuticals for human use
ICH Q1E guideline	Guideline on Evaluation of Stability Data (PMSB/ELD Notification No. 0603004 dated June 3, 2003)
Impurity C	[redacted]
IR	Infrared absorption spectrum
K_b	Binding constant
K_i	Inhibition constant
K_{obs}	Observed association rate constant
K_{off}	Dissociation rate constant
LC/MS/MS	Liquid chromatography tandem mass spectrometry
MACE	Major adverse cardiac events
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MS	Mass spectrum
Naldemedine	Naldemedine Tosilate
Naldemedine 3-G	Naldemedine 3-O-β-D-glucuronide
Naldemedine 6-G	Naldemedine 6-O-β-D-glucuronide
Naldemedine-CA	Naldemedine-carboxylic acid
NMR	Nuclear magnetic resonance spectrum
NRS	Numerical rating scale
OAT	Organic anion transporter

OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OIC	Opioid-induced constipation
PAC-QOL	Patient assessment of constipation-Quality of life
PAC-SYM	Patient assessment of constipation symptoms
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per protocol set
PS	Performance status
PTP	Press through package
QbD	Quality by design
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
RH	Relative humidity
SBM	Spontaneous bowel movement (without the use of a rescue laxative medication during the 24 hours prior to the BM)
$t_{1/2}$	Elimination half-life
t_{max}	Time to reach maximum plasma concentration
UGT	Uridine diphospho-glucuronosyl transferase
UV	Ultraviolet-visible absorption spectrum
U-50488H	trans-3,4-dichloro-N-methyl-N[2(pyrrolidinyl)-cyclohexyl]-benzeneacetamide
WBP	Whole body plethysmography
ΔΔQTcF	Placebo-adjusted change from baseline in QTcF

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Opioids have been used for the management of moderate to severe pain, including cancer pain treatment. Major opioid analgesics include morphine hydrochloride, oxycodone hydrochloride, and fentanyl citrate. While exerting analgesic effects via μ-opioid receptors in the central nervous system, these opioids inhibit gastrointestinal motility and suppress enteric neural activity via peripheral μ-opioid receptors in the gastrointestinal tract, leading to opioid-induced constipation (OIC) (*Drugs.* 2012; 72: 1847-1865). As patients receiving opioids frequently experience OIC, the management of OIC is important during pain management with opioids (*J Med Econ*. 2013; 16: 1423-1433, *Pain*. 2004; 112: 372-380, etc.).

In Japan, as drugs for the treatment of OIC, osmotic laxatives (magnesium oxide, lactulose), large-bowel stimulant laxatives (sennoside, sodium picosulfate hydrate), etc. are used alone or in combination ("Guideline on drug therapy for cancer pain 2014" Japanese Society for Palliative Medicine ed.). These drugs, however, have problems: that osmotic laxatives may lead to abnormal electrolytes including hypermagnesaemia and bloating; and that chronic use of large-bowel stimulant laxatives may result in tolerance or habituation.

Naldemedine Tosilate (hereinafter referred to as naldemedine) is a peripherally-acting μ-opioid receptor antagonist discovered by the applicant. The development of naldemedine was initiated because naldemedine was expected to improve OIC by antagonizing the peripheral gastrointestinal effects of opioids without affecting μ-opioid receptors in the central nervous system.

As of November 2016, naldemedine is not approved in any country.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to light tan powder. The following general properties of the drug substance have been determined: description, thermal analysis, pH, acid dissociation constant, partition coefficient, optical rotation, solubility, hygroscopicity, and crystalline polymorphism. Crystalline form I ([redacted]) only is produced by the drug substance manufacturing process.

Its chemical structure has been elucidated by elemental analysis, MS, IR, UV, and NMR (^{1}H-NMR and ^{13}C-NMR).

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted] and [redacted] as starting materials.

A quality control strategy was developed with a QbD approach, based on the following studies.

- The following have been identified as CQAs: related substances, [redacted], residual solvents, [redacted], crystalline form, description, identification, content, p-toluenesulfonic acid, optical rotation, water content, residue on ignition, and metals.
- CPPs have been identified through quality risk assessment and design of experiments.

[redacted] and [redacted] have been defined as critical steps. [redacted] has been defined as a critical intermediate.

2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of content, description, identification (UV, IR), purity (related substances [HPLC], residual solvents [GC]), water content, residue on ignition, [redacted], and assay (HPLC).

2.1.4 Stability of drug substance

The primary stability studies on the drug substance are presented in Table 1. The photostability study showed that the drug substance is photostable.

Table 1. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 pilot-scale batches	30℃	65%RH	Double low-density polyethylene bags and a plastic cable tie	36 months
Accelerated		40℃	75%RH		6 months

Based on the above, a retest period of [redacted] months was proposed for the drug substance when stored in double low-density polyethylene bags at room temperature. The long-term testing will be continued up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an immediate-release film-coated tablet containing 0.2604 mg of naldemedine tosilate (equivalent to 0.2 mg of naldemedine) and the following excipients: D-mannitol, croscarmellose sodium, magnesium stearate, hypromellose, talc, and yellow ferric oxide.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of [redacted], [redacted], coating, filling/labeling/packaging, and testing/storage. [redacted], [redacted], [redacted], and [redacted] have been defined as critical steps.

A quality control strategy was developed with a QbD approach, based on the following studies.

- CQAs, CMAs, and CPPs have been identified through quality risk assessment and the results of experiments; and a control strategy has been developed.

- The following have been identified as CQAs: strength, related substances, uniformity of dosage units, appearance, and [redacted].

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (HPLC/UV), purity (related substances [HPLC]), [redacted], uniformity of dosage units (content uniformity), dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

The primary stability studies on the drug product are presented in Table 2. The photostability study showed that the drug product is photosensitive.

Table 2. Stability studies on drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	25°C	60%RH	PTP + aluminum bag	24 months
Accelerated		40°C	75%RH		6 months

Based on the above, in accordance with the ICH Q1E guideline, a shelf-life of 36 months was proposed for the drug product when stored at room temperature, protected from light, in a PTP sheet packaged in an aluminum bag. The long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Primary pharmacodynamic studies were conducted to evaluate the effects of naldemedine on opioid receptors and improvement of opioid-induced constipation. Secondary pharmacodynamic studies were conducted to investigate the inhibitory effects of naldemedine on receptors other than opioid receptors, the effects of its metabolites on opioid receptors, and the influence of naldemedine on opioid analgesic effect. Safety pharmacology studies were conducted to assess the effects of naldemedine on the central nervous, cardiovascular, and respiratory systems. All doses and concentrations of naldemedine in the studies are expressed as free base. Unless otherwise specified, 0.5% methylcellulose aqueous solution was used as vehicle.

3.1 Primary pharmacodynamics

3.1.1 Effects on opioid receptors

3.1.1.1 Binding affinities and antagonistic activities for human opioid receptors (CTD 4.2.1.1-01 and 4.2.1.1-02, Study IDs R-297995-EB-074-N and S-297995-EF-284-N)

Membrane fractions of CKO-K1 cells transfected with recombinant human μ, δ, and κ receptors, were used to determine the inhibitory activities of naldemedine against radioligand binding to recombinant human μ, δ, and κ receptors. The inhibition constants (K_i values) (mean ± standard error [SE]) of naldemedine for recombinant

human μ, δ, and κ receptors were 0.34 ± 0.03, 0.43 ± 0.08, and 0.94 ± 0.08 nmol/L, respectively, showing that naldemedine had binding affinities for these opioid receptors.

The concentrations of naldemedine producing 50% inhibition of recombinant human μ, δ, and κ receptor activation by their corresponding agonists (K_b values) (mean ± SE) were 0.50 ± 0.05, 0.27 ± 0.03, and 0.44 ± 0.08 nmol/L, respectively; naldemedine thus exhibited antagonistic activities against these opioid receptors. DAMGO, [Met^5]-enkephalin, and U-50488H were used as μ, δ, and κ receptor agonists, respectively.

3.1.1.2 Mode of opioid receptor inhibition (CTD 4.2.1.1-05, 4.2.1.1-06, and 4.2.1.1-12, Study IDs S-297995-EB-224-N, S-297995-EB-222-N, and R-297995-EB-311-R [Reference data])

The observed association rate constants (K_{obs}) of naldemedine for human and recombinant rat μ opioid receptors were 0.045 ± 0.002 and 0.070 ± 0.006 min^{-1}, respectively, and the dissociation rate constants (K_{off}) were 0.023 ± 0.000 and 0.016 ± 0.000 min^{-1}, respectively.

The inhibitory effects of naldemedine on recombinant human μ-opioid receptor activation induced by μ-opioid receptor agonists (i.e., morphine hydrochloride, oxycodone hydrochloride, hydrocodone bitartrate, and fentanyl citrate) were investigated. Naldemedine exhibited non-competitive inhibition of μ-opioid receptor activation by these agonists.

3.1.2 Improvement of opioid-induced constipation

3.1.2.1 Antagonistic effect on morphine hydrochloride-induced suppression of small intestinal transit in rats (CTD 4.2.1.1-07 and 4.2.1.1-09, Study IDs R-297995-EB-071-N and S-297995-EB-221-N)

A single oral dose of naldemedine 0.01 to 10 mg/kg or vehicle was administered to fasted male rats, followed by 3 mg/kg of subcutaneous morphine hydrochloride 15 minutes later. At 30 minutes after administration of morphine hydrochloride, 0.5% Evans blue suspension was given intragastrically, and 15 minutes later, the distance traveled by Evans blue was calculated as a percentage of the total length of the small intestine[1)] (Table 3). Naldemedine 0.03 to 10 mg/kg significantly antagonized morphine hydrochloride-induced suppression of small intestinal transit, compared with vehicle control; the ED_{50} value of naldemedine was 0.03 mg/kg.

Table 3. Percentage of the maximal possible effect (MPE) on morphine hydrochloride 3 mg/kg-induced suppression of small intestinal transit in rats

Treatment group		% MPE
Vehicle control		0.01 ± 9.50
Naldemedine (mg/kg)	0.01	12.49 ± 11.46
	0.03	41.28 ± 11.40*
	0.1	71.07 ± 5.87**
	0.3	88.54 ± 12.76**
	1	91.50 ± 8.22**
	3	90.55 ± 8.63**
	10	110.65 ± 6.44**

Mean ± SE, n = 10
*P < 0.05, **P < 0.01 (vs. vehicle control, Dunnett's test)

1) The mean difference in the distance traveled by Evans blue between the vehicle control (vehicle + morphine hydrochloride) group and the vehicle + saline (instead of morphine hydrochloride) group was taken as 100% (the maximal possible effect).

A single oral dose of naldemedine 0.01 to 10 mg/kg or vehicle was administered to fasted male rats, followed by 20 mg/kg of oral morphine hydrochloride 15 minutes later. At 30 minutes after administration of morphine hydrochloride, 0.5% Evans blue suspension was given intragastrically, and 15 minutes later, the distance traveled by Evans blue was calculated as a percentage of the total length of the small intestine[1)] (Table 4). Naldemedine 0.1 to 10 mg/kg significantly antagonized morphine hydrochloride-induced suppression of small intestinal transit, compared with vehicle control; the ED_{50} value of naldemedine was 0.23 mg/kg.

Table 4. Percentage of MPE on morphine hydrochloride 20 mg/kg-induced suppression of small intestinal transit in rats

Treatment group		% MPE
Vehicle control		0.01 ± 3.86
Naldemedine (mg/kg)	0.01	15.79 ± 4.77
	0.03	13.54 ± 7.49
	0.1	39.97 ± 5.16**
	0.3	56.17 ± 10.39**
	1	80.57 ± 6.03**
	3	85.57 ± 6.61**
	10	96.88 ± 5.57**

Mean ± SE, n = 12
**P < 0.01 (vs. vehicle control, Dunnett's test)

3.1.2.2 Antagonistic effect on the inhibitory effect of morphine hydrochloride on castor oil-induced diarrhea in rats (CTD 4.2.1.1-10, Study ID R-297995-EB-092-N)

A single oral dose of naldemedine 0.003 to 1 mg/kg or vehicle was administered to fasted male rats, and 45 minutes later, castor oil was administered intragastrically. Morphine hydrochloride 1 mg/kg was administered subcutaneously at 15 minutes after administration of castor oil. The rats were observed for castor oil-induced diarrhea for 1 hour. The symptoms of diarrhea were scored (0, without diarrhea; 1, mild diarrhea containing loose bowels; 2, intense liquefied diarrhea). The results are shown in Table 5.

Naldemedine 0.03 to 1 mg/kg significantly antagonized the inhibitory effect of morphine hydrochloride on castor oil-induced diarrhea, compared with vehicle control; the ED_{50} value of naldemedine was 0.01 mg/kg.

Table 5. Incidence of castor oil-induced diarrhea in rats following administration of morphine hydrochloride 1 mg/kg

Treatment group		Incidence of diarrhea symptoms (%)		
		Score 1	Score 2	Total
Vehicle control		0	0	0
Naldemedine (mg/kg)	0.003	0	0	0
	0.01	18	27	45
	0.03	18	82	100**
	0.1	0	100	100**
	0.3	0	100	100**
	1	0	100	100**

n = 11
**P < 0.01 (vs. vehicle control, Steel's multiple comparison test)

3.1.2.3 Antagonistic effect on oxycodone hydrochloride-induced suppression of small intestinal transit in rats (CTD 4.2.1.1-08, Study ID S-297995-EF-260-N)

A single oral dose of naldemedine 0.001 to 3 mg/kg or vehicle was administered to fasted male rats, followed by 1 mg/kg of subcutaneous oxycodone hydrochloride 30 minutes later. At 15 minutes after administration of oxycodone hydrochloride, 0.5% Evans blue suspension was administered intragastrically, and 15 minutes later, the distance traveled by Evans blue was calculated as a percentage of the total length of the small intestine[1)] (Table 6). Naldemedine 0.03 to 3 mg/kg significantly antagonized oxycodone hydrochloride-induced suppression of small intestinal transit, compared with vehicle control; the ED_{50} value of naldemedine was 0.02 mg/kg.

Table 6. Percentage of MPE on oxycodone hydrochloride 1 mg/kg-induced suppression of small intestinal transit in rats

Treatment group		% MPE
Vehicle control		0.01 ± 4.42
Naldemedine (mg/kg)	0.001	9.90 ± 8.15
	0.003	20.19 ± 6.82
	0.01	21.46 ± 9.93
	0.03	60.99 ± 6.16**
	0.1	64.77 ± 7.44**
	0.3	73.62 ± 5.00**
	1	83.79 ± 4.44**
	3	89.50 ± 3.96**

Mean ± SE; n = 10
** $P < 0.01$ (vs. vehicle control, Dunnett's test)

3.2 Secondary pharmacodynamics

3.2.1 Selectivity study (CTD 4.2.1.2-01, Study ID R-297995-EF-081-N)

The inhibitory effects of naldemedine 10 μmol/L on 62 receptors, ion channels, and transporters, etc. were investigated. Naldemedine did not induce a ≥50% inhibition of any receptors, ion channels, or transporters, except for opioid receptors.

3.2.2 Effects of metabolites (CTD 4.2.1.1-02 and 4.2.1.2-09, Study IDs R-297995-EF-284-N and S-297995-EB-135-N)

Table 7 and Table 8 show the K_i and K_b values, respectively, of 5 major metabolites of naldemedine (nor-naldemedine, naldemedine 3-G, naldemedine 6-G, naldemedine-CA, benzamidine) for recombinant human μ, δ, and κ receptors. Relative to unchanged naldemedine, all metabolites showed less potent binding affinities and antagonistic activities against opioid receptors.

Table 7. K_i values of metabolites for recombinant human μ, δ, and κ receptors

Test compound	K_i value (nmol/L)		
	μ receptor	δ receptor	κ receptor
Nor-naldemedine	1.95 ± 0.28	10.23 ± 3.01	61 ± 13
Naldemedine 3-G	191.78 ± 33.39	158.59 ± 38.14	915 ± 320
Naldemedine 6-G	9.79 ± 1.03	0.51 ± 0.06	36 ± 8
Naldemedine-CA	7.38 ± 1.10	2.05 ± 0.96	151 ± 33
Benzamidine	> 2644	> 2943	> 6250

Mean ± SE

Table 8. K_b values of metabolites for recombinant human μ, δ, and κ receptors

Test compound	K_b value (nmol/L)		
	μ receptor	δ receptor	κ receptor
Nor-naldemedine	31.65 ± 10.76	112.36 ± 10.65	> 270.68
Naldemedine 3-G	> 42.41	301.13 ± 110.67	> 270.68
Naldemedine 6-G	15.53 ± 0.98	0.70 ± 0.20	28.5 ± 7.28
Naldemedine-CA	14.11 ± 3.24	6.11 ± 1.32	201 ± 13.3
Benzamidine	ND [a)]	ND [a)]	> 270.68

Mean ± SE

a) Not determined because benzamidine had no binding affinities for recombinant human μ and δ receptors.

3.2.3 Influence on opioid analgesic effect (CTD 4.2.1.2-02, 4.2.1.2-03, and 4.2.1.2-04, Study IDs R-297995-EB-072-N, S-297995-EB-181-N, and S-297995-EB-274-N)

The analgesic effect of morphine hydrochloride was evaluated by tail-flick test in male rats at 1 hour after a single oral administration of naldemedine 1, 3, 10, or 30 mg/kg or vehicle. Morphine hydrochloride 6 mg/kg was administered subcutaneously 45 minutes before the test. Naldemedine at any dose level did not influence the analgesic effect of morphine hydrochloride, compared with vehicle control.

A single oral dose of naldemedine 3, 5, 7, 10, or 30 mg/kg or vehicle was administered to male rats. Tail-flick test was conducted to evaluate the analgesic effect of morphine hydrochloride up to 24 hours after administration of naldemedine or vehicle. Morphine hydrochloride 6 mg/kg was administered subcutaneously 45 minutes before each test. Compared with vehicle control, 10 and 30 mg/kg of naldemedine significantly inhibited the analgesic effect of morphine hydrochloride at 6 hours post-dose (10 mg/kg) and at 4, 6, and 8 hours post-dose (30 mg/kg).

A single oral dose of naldemedine 1, 3, 5, or 7 mg/kg or vehicle was administered to post-operative pain model rats. Tail-flick test was conducted to evaluate the analgesic effect of morphine hydrochloride up to 8 hours after administration of naldemedine or vehicle. The rat model of post-operative pain was established by suturing an incision that had been made through skin and fascia of the plantar aspect of hind paw of male rats. Morphine hydrochloride 6 mg/kg was administered subcutaneously 45 minutes before each test. Compared with vehicle control, 5 and 7 mg/kg of naldemedine significantly inhibited the analgesic effect of morphine hydrochloride at 6 hours post-dose (5 mg/kg) and at 4, 6, and 8 hours post-dose (7 mg/kg).

3.3 Safety pharmacology

The results from safety pharmacology studies were submitted (Table 9).

Table 9. Summary of safety pharmacology studies

Organ systems evaluated	Test system	Endpoints/Method of assessment	Doses	Route of adminis-tration	Findings	CTD (Study ID)
CNS	Rat (6 males/group)	FOB	30, 100, 300 mg/kg	Oral	Naldemedine at doses up to 300 mg/kg had no effects.	4.2.1.3-03 (R-297995-SF-075-L)
Respiratory system	Rat (8 males/group)	WBP (respiratory rate, tidal volume, minute volume)	30, 100, 300 mg/kg	Oral	Naldemedine at doses up to 300 mg/kg had no effects.	4.2.1.3-04 (R-297995-SF-077-L)
Cardiovascular system	Dog (4 males/group)	blood pressure, heart rate, ECG (conscious)	10, 30, 100 mg/kg	Oral	Naldemedine at doses up to 100 mg/kg had no effects on blood pressure, heart rate, or ECG. Emesis was observed at 4 hours post-dose in 1 dog at 30 mg/kg and at 1 hour post-dose in 4 dogs at 100 mg/kg, but all events were transient.	4.2.1.3-05 (R-297995-SF-076-L)
	Isolated guinea pig papillary muscles (5 preparations/group)	APD	0.3, 3, 30 µmol/L	*In vitro*	Naldemedine 30 µmol/L prolonged APD_{90} and APD_{30-90} (the difference between APD_{90} and APD_{30}) by ≥10% (>10,000-fold safety margin)	4.2.1.3-01 (R-297995-SF-078-L)
	HEK293 cells (5 preparations/group)	hERG current	0.3, 3, 30 µmol/L	*In vitro*	Naldemedine inhibited hERG current by 3.2%, 5.6%, and 33.1% at 0.3, 3, and 30 µmol/L, respectively (IC_{50} value >30 µmol/L).	4.2.1.3-02 (R-297995-SF-079-L)

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological effects

The applicant's explanation on the pharmacological effects of naldemedine:

Opioid analgesics, such as morphine hydrochloride and oxycodone hydrochloride, exert their actions predominantly via μ-opioid receptors in the central nervous system while they cause constipation etc. by slowing gastrointestinal motility and suppressing enteric neural activity via peripheral μ-opioid receptors in the gastrointestinal tract (*Drugs*. 2012; 72: 1847-1865).

The submitted primary pharmacodynamic data show that naldemedine has antagonistic activities against μ, δ, and κ receptors. Moreover, naldemedine dose-dependently antagonized small intestinal transit suppression induced by subcutaneous morphine hydrochloride or subcutaneous oxycodone hydrochloride. The drug also antagonized small intestinal transit suppression induced by oral morphine hydrochloride. Based on the above, regardless of type or route of administration of opioids, naldemedine can prevent opioid-induced suppression of small intestinal transit by binding to μ-opioid receptors in the gastrointestinal tract and antagonizing the peripheral effects of opioids.

Based on the submitted primary pharmacodynamic data, PMDA considers that naldemedine exerts anti-constipating effects in the treatment of opioid-induced constipation.

3.R.2 Influence on opioid analgesic effect

The applicant's explanation on the influence of naldemedine on opioid analgesic effect:

The analgesic effect of subcutaneous morphine hydrochloride was not affected by a single oral dose of naldemedine at doses up to 7 mg/kg in the rat tail-flick test and at doses up to 3 mg/kg in the rat post-operative pain model. The C_{max} (mean ± standard deviation [SD]) at the no-observed-effect-level (NOEL) (3 mg/kg) in rats was 282 ± 45 ng/mL. The C_{max} values at the clinical dose (0.2 mg/day) were 2.02 ng/mL in Japanese patients with cancer and 2.00 ng/mL in non-Japanese patients with chronic non-cancer pain.[2)] Hence, naldemedine is unlikely to influence opioid analgesic effect in clinical use.

PMDA accepted the applicant's explanation.

3.R.3 Safety pharmacology studies

PMDA considers that, since no particular problems have been identified from the safety pharmacology data submitted, naldemedine is unlikely to exhibit significant pharmacological effects on the central nervous, respiratory, or cardiovascular system in clinical use.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Pharmacokinetics were studied in rats and dogs following intravenous or oral administration of naldemedine or ^{14}C-naldemedine. Plasma concentrations of unchanged naldemedine and its metabolites (nor-naldemedine, naldemedine 3-G, and benzamidine[3)]) were determined by high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS). The lower limit of quantification (LLOQ) in rat plasma was 0.5 ng/mL (CTD 4.2.2.2-03) and 0.01 ng/mL (CTD 4.2.2.2-06) for unchanged naldemedine and 0.04 ng/mL for nor-naldemedine and naldemedine 3-G (CTD 4.2.2.2-06). The LLOQ in dog plasma was 0.5 ng/mL (CTD 4.2.2.2-11) and 20.0 ng/mL (CTD 4.2.3.2-04 and 4.2.3.2-06) for unchanged naldemedine, 20.0 ng/mL for nor-naldemedine and naldemedine 3-G, and 0.5 ng/mL for benzamidine (CTD 4.2.3.2-06). [^{14}C]-naldemedine-derived radioactivity was measured using liquid scintillation counter.

The results from the main studies are described below. Section 6.1.2 discusses the metabolism of naldemedine.

4.1 Absorption

4.1.1 Single-dose studies

4.1.1.1 Single oral and intravenous dose studies in rats and dogs (CTD 4.2.2.2-03 and 4.2.2.2-11, R-297995-PB-070-N and S-297995-PB-161-N)

Table 10 and Table 11 show the plasma pharmacokinetic parameters of unchanged naldemedine following a single oral or intravenous administration of naldemedine to male rats and male dogs under non-fasted

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2) The C_{max} data in Japanese patients with cancer were obtained from a multi-regional (Japan and Korea) late phase II dose-finding study in patients with cancer (Study V9222). Because there are no clinical study data to calculate pharmacokinetic parameters from plasma concentrations in Japanese patients with chronic non-cancer pain, C_{max} data in non-patients with chronic non-cancer pain were used (data obtained from a foreign late phase II dose-finding study in patients with chronic pain [Study V9221]).

3) Benzamidine is not formed in human hepatocytes, and naldemedine and its metabolites in bile (nor-naldemedine and naldemedine 3-G) were unstable in rat feces. The applicant thus explained that benzamidine appeared to be produced by enterobacteria.

conditions. In rats and dogs, the $AUC_{0\text{-}inf}$ and C_{max} increased in an almost dose-proportional manner over the dose range of 0.3 to 3 mg/kg.

Table 10. Plasma pharmacokinetic parameters of unchanged naldemedine following a single oral or intravenous administration in rats

Route of administration	Naldemedine dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)	BA[a)] (%)
Oral	0.3	19 ± 5	0.88 ± 0.25	68 ± 24	1.87 ± 0.63	32.1 ± 11.4
	1	38 ± 3	1.00 ± 0.00	172 ± 33	1.89 ± 0.54	24.5 ± 4.7
	3	168 ± 48	1.13 ± 0.63	674 ± 166	1.66 ± 0.55	32.0 ± 7.9
	10	853 ± 175	0.63 ± 0.25	2650 ± 220	1.34 ± 0.34	37.7 ± 3.2
Intravenous	0.5	—	—	351 ± 29	1.02 ± 0.15	—
	1	—	—	725 ± 61	1.27 ± 0.19	—

n = 4; Mean ± SD;
—: not calculated
a) Calculated using the $AUC_{0\text{-}inf}$ following intravenous administration of 0.5 mg/kg naldemedine.

Table 11. Plasma pharmacokinetic parameters of unchanged naldemedine following a single oral or intravenous administration in dogs

Route of administration	Naldemedine dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)	BA[a)] (%)
Oral	0.3	58 ± 36	1.75 ± 1.50	291 ± 45	3.14 ± 0.93	48.9 ± 4.0
	1	213 ± 81	1.38 ± 1.75	989 ± 127	2.36 ± 0.61	49.9 ± 3.5
	3	963 ± 346	1.63 ± 1.60	3700 ± 500	1.70 ± 0.22	62.4 ± 7.9
	10	4110 ± 630	1.13 ± 0.63	19,500 ± 2800	2.26 ± 0.08	98.6 ± 11.2
Intravenous	0.5	—	—	989 ± 72	1.28 ± 0.03	—
	1	—	—	1970 ± 190	1.24 ± 0.03	—

n = 4; Mean ± SD
—: not calculated
a) Calculated using the $AUC_{0\text{-}inf}$ following intravenous administration of 0.5 mg/kg naldemedine.

4.1.1.2 Plasma concentrations of unchanged naldemedine and its metabolites following single oral administration in rats (CTD 4.2.2.2-06, S-297995-PF-197-N)

Table 12 shows the plasma pharmacokinetic parameters of unchanged naldemedine and its metabolites following a single oral administration of naldemedine to male rats under fasted conditions.

Table 12. Plasma pharmacokinetic parameters of unchanged naldemedine and its metabolites following single oral administration in rats

Naldemedine dose (mg/kg)	Compound	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
1	Unchanged naldemedine	77.6 ± 36.1	0.75 ± 0.84	270 ± 36	7	697 ± 214	0.88 ± 0.25	2460 ± 330
	Nor-naldemedine	3.9 ± 1.4	1.63 ± 1.60	22.3 ± 4.8		43.8 ± 14.1	1.00 ± 0.00	179 ± 37
	Naldemedine 3-G	3.1 ± 1.6	0.44 ± 0.13	6.2 ± 1.2		18.6 ± 5.3	0.69 ± 0.38	45.7 ± 5.7
3	Unchanged naldemedine	282 ± 45	0.81 ± 0.80	1110 ± 330	10	915 ± 90	1.88 ± 1.55	4000 ± 930
	Nor-naldemedine	16.9 ± 1.9	0.75 ± 0.29	73.9 ± 14.2		51.5 ± 4.7	1.88 ± 1.55	249 ± 60
	Naldemedine 3-G	10.6 ± 3.7	0.50 ± 0.00	20.8 ± 6.4		22.9 ± 7.6	0.88 ± 0.75	66.5 ± 27.8
5	Unchanged naldemedine	518 ± 73	0.56 ± 0.32	1940 ± 350	30	3260 ± 720	3.00 ± 1.15	15,700 ± 2900
	Nor-naldemedine	36.6 ± 5.9	1.00 ± 0.00	146 ± 28		193 ± 26	3.00 ± 1.15	1050 ± 90
	Naldemedine 3-G	16.2 ± 3.9	0.63 ± 0.25	40.6 ± 16.5		51.4 ± 16.6	3.00 ± 1.51	228 ± 40

n = 4; Mean ± SD

4.1.2 Repeated-dose studies (CTD 4.2.3.2-04 and 4.2.3.2-06, R-297995-TB-046-L and S-297995-TF-219-L)

The toxicokinetics of naldemedine following oral administration of naldemedine for 30 days or 9 months in male and female dogs were evaluated in toxicity studies. Table 13 and Table 14 show the plasma pharmacokinetic parameters of unchanged naldemedine and its metabolites following once-daily oral administration of naldemedine for 30 days or 9 months in male and female dogs. In the 30-day repeated oral dose study, the $AUC_{0\text{-}24h}$ and C_{max} of unchanged naldemedine increased in a dose-proportional manner over the dose range of 1 to 3 mg/kg/day and increased more than dose-proportionally over the dose range of 3 to 50 mg/kg/day. In the 9-month repeated oral dose study, the $AUC_{0\text{-}24h}$ and C_{max} of unchanged naldemedine increased in a dose-proportional manner over the dose range of 1 to 4 mg/kg/day and increased more than dose-proportionally over the dose range of 4 to 20 mg/kg/day. The $AUC_{0\text{-}24h}$ and C_{max} of benzamidine also increased dose-proportionally. No gender-related differences were observed.

Table 13. Plasma pharmacokinetic parameters of unchanged naldemedine and its metabolites following 30-day oral administration in dogs

Naldemedine dose (mg/kg/day)	Compound		Male		Female	
			C_{max} (μg/mL)	$AUC_{0\text{-}24h}$ (μg·h/mL)	C_{max} (μg/mL)	$AUC_{0\text{-}24h}$ (μg·h/mL)
1	Unchanged naldemedine	Day 1	0.65 ± 0.08	1.01 ± 0.28	0.64 ± 0.19	1.02 ± 0.21
		Day 30	0.52 ± 0.07	1.26 ± 0.51	0.57 ± 0.18	1.27 ± 0.48
	Nor-naldemedine	Day 1	NC	NC	NC	NC
		Day 30	NC	NC	NC	NC
	Naldemedine 3-G	Day 1	NC	NC	NC	NC
		Day 30	NC	NC	NC	NC
3	Unchanged naldemedine	Day 1	1.92 ± 0.58	3.63 ± 1.12	1.80 ± 0.15	2.81 ± 0.23
		Day 30	2.29 ± 0.39	5.03 ± 0.53	2.04 ± 0.29	4.24 ± 0.73
	Nor-naldemedine	Day 1	0.06 ± 0.01	0.08 ± 0.03	0.06 ± 0.01	0.06 ± 0.01
		Day 30	0.05 ± 0.01	0.09 ± 0.03	0.05 ± 0.02	0.08 ± 0.03
	Naldemedine 3-G	Day 1	NC	NC	NC	NC
		Day 30	NC	NC	NC	NC
10	Unchanged naldemedine	Day 1	5.78 ± 2.77	18.40 ± 11.83	6.78 ± 1.74	15.37 ± 1.16
		Day 30	6.48 ± 2.32	23.95 ± 12.97	7.47 ± 1.98	19.60 ± 1.15
	Nor-naldemedine	Day 1	0.16 ± 0.02	0.43 ± 0.08	0.34 ± 0.29	0.64 ± 0.49
		Day 30	0.13 ± 0.01	0.41 ± 0.04	0.11 ± 0.01	0.30 ± 0.07
	Naldemedine 3-G	Day 1	NC	NC	0.02 ± 0.02	0.01 ± 0.01
		Day 30	0.02 ± 0.02	0.02 ± 0.02	0.03 ± 0.01	0.02 ± 0.01
50	Unchanged naldemedine	Day 1	31.04 ± 25.52	93.86 ± 20.10	21.16 ± 3.18	98.29 ± 20.38
		Day 30	20.12 ± 3.64	142.80 ± 57.46	22.24 ± 5.23	130.09 ± 43.86
	Nor-naldemedine	Day 1	0.78 ± 0.58	2.47 ± 0.56	0.64 ± 0.15	2.59 ± 0.68
		Day 30	0.78 ± 0.40	7.00 ± 7.79	0.54 ± 0.07	2.89 ± 0.33
	Naldemedine 3-G	Day 1	0.16 ± 0.11	0.37 ± 0.25	0.12 ± 0.07	0.31 ± 0.20
		Day 30	0.51 ± 0.51	3.46 ± 4.38	0.19 ± 0.04	0.78 ± 0.45

Mean ± SD; n = 3 (n = 5 in the 50 mg/kg group only)
NC: not calculated because of concentrations below the LLOQ (< 0.02 μg/mL)

Table 14. Plasma pharmacokinetic parameters of unchanged naldemedine and its metabolites following 9-month oral administration in dogs

Naldemedine dose (mg/kg/day)	Compound		Male		Female	
			C_{max} (μg/mL)	$AUC_{0\text{-}24h}$ (μg·h/mL)	C_{max} (μg/mL)	$AUC_{0\text{-}24h}$ (μg·h/mL)
1	Unchanged naldemedine	Day 1	0.42 ± 0.03	0.74 ± 0.10	0.43 ± 0.04	1.04 ± 0.13
		Day 273	0.30 ± 0.07	0.71 ± 0.09	0.40 ± 0.14	0.99 ± 0.24
	Benzamidine	Day 1	0.00 ± 0.00	0.04 ± 0.01	0.00 ± 0.00	0.04 ± 0.01
		Day 273	0.00 ± 0.00	0.07 ± 0.01	0.01 ± 0.00	0.07 ± 0.02
4	Unchanged naldemedine	Day 1	2.25 ± 0.29	4.08 ± 0.62	2.16 ± 0.49	5.87 ± 1.09
		Day 273	2.32 ± 0.37	5.85 ± 1.56	1.90 ± 0.32	5.97 ± 0.76
	Benzamidine	Day 1	0.01 ± 0.002	0.15 ± 0.04	0.01 ± 0.001	0.13 ± 0.02
		Day 273	0.02 ± 0.00	0.30 ± 0.06	0.01 ± 0.00	0.16 ± 0.05
20	Unchanged naldemedine	Day 1	8.04 ± 1.03	36.7 ± 11.9	8.74 ± 2.99	33.6 ± 13.4
		Day 273	10.0 ± 2.2	55.9 ± 18.8	8.35 ± 2.03	40.5 ± 14.0
	Benzamidine	Day 1	0.08 ± 0.01	1.07 ± 0.26	0.06 ± 0.03	0.78 ± 0.29
		Day 273	0.08 ± 0.03	1.39 ± 0.63	0.08 ± 0.03	1.35 ± 0.40

Mean ± SD, n = 4

4.2 Distribution

4.2.1 Tissue distribution in rats (CTD 4.2.2.3-01 and 4.2.2.3-04, Study IDs R-297995-PB-057-N and S-297995-PF-213-N)

Male albino rats (n = 1/time point) received a single oral dose of [^{14}C]-naldemedine 1 mg/kg, and tissue radioactivity concentrations were determined at 0.25, 1, 4, 8, 24, and 72 hours post-dose.[4)] In most tissues, radioactivity concentrations peaked at 1 hour post-dose and then decreased over time. At 1 hour post-dose, radioactivity concentrations were high in the adrenal gland, liver, renal cortex, and submaxillary gland (2.5, 11.4, 2.6, and 2.4 times, respectively, the plasma concentration). Radioactivity was not detected in the brain at any time point. The blood to plasma radioactivity concentration ratio peaked at 8 hours post-dose (1.25 to 2.32).

Radioactivity concentrations following a single oral dose of [^{14}C]-naldemedine 1 mg/kg in male pigmented rats were similar to the above results, and naldemedine had no affinity for melanin.

4.2.2 Placental transfer in rats (CTD 4.2.2.3-05, Study ID S-297995-PF-238-N)

Pregnant rats received a single oral dose of [^{14}C]-naldemedine 1 mg/kg on gestation day 18, and concentrations of radioactivity in maternal and fetal tissues were determined. In most tissues, radioactivity concentrations peaked at 1 to 2 hours post-dose and then decreased over time. Radioactivity was transferred to fetal tissues, but its concentrations in fetal tissues were lower than those in maternal whole blood at all time points and decreased below the LLOQ by 24 hours post-dose.

4) Concentrations of radioactivity in the following tissues/organs were determined: blood, plasma, adrenal gland, blood (in the heart, in the hepatic vein, in the portal vein, in the renal vein), bone marrow, fat (brown fat, white fat), cervical lymph node, cerebellum, cerebrum, exorbital lacrimal gland, Harderian gland, heart, hypophysis, intestinal wall, liver, lung, pancreas, parotid gland, pineal body, preputial gland, prostate, rectal mucosa, renal cortex, renal cortico medullary, renal medulla, seminal vesicle, skeletal muscle, skin, spinal cord, spleen, submaxillary gland, testis, thymus, and thyroid.

4.3 Excretion

4.3.1 Urinary, fecal, and biliary excretion in rats (CTD 4.2.2.5-01 and 4.2.2.5-02, Study IDs R-297995-PB-025-N and R-297995-PB-098-N)

Male rats received single oral doses of 2 types of [^{14}C]-naldemedine 1 mg/kg. Cumulative urinary and fecal excretion of radioactivity is shown in Table 15.

Table 15. Cumulative urinary and fecal excretion following a single dose of [^{14}C]-naldemedine 1 mg/kg

	No. of animals	Time point	Cumulative urinary excretion (%)	Cumulative fecal excretion (%)
[Oxadiazole-^{14}C]-naldemedine	5	168 hours	49.2 ± 2.4	49.1 ± 2.6
[Carbonyl-^{14}C]-naldemedine	4	168 hours	1.5 ± 0.2	97.4 ± 0.4

Mean ± SD

Bile duct cannulated rats received single oral doses of 2 types of [^{14}C]-naldemedine 1 mg/kg. Cumulative urinary, fecal, and biliary excretion of radioactivity is shown in Table 16.

Table 16. Cumulative urinary, fecal, and biliary excretion following a single dose of [^{14}C]-naldemedine 1 mg/kg in bile duct cannulated rats

	No. of animals	Time point	Cumulative urinary excretion (%)	Cumulative fecal excretion (%)	Cumulative biliary excretion (%)
[Oxadiazole-^{14}C]-naldemedine	4	48 hours	44.8 ± 8.9	24.4 ± 2.6	28.2 ± 6.9
[Carbonyl-^{14}C]-naldemedine	5	48 hours	2.5 ± 0.9	57.6 ± 16.2	31.3 ± 11.1

Mean ± SD

The above results showed that following oral administration of [oxadiazole-^{14}C]-naldemedine to rats, the absorbed radioactivity is excreted predominantly in urine and also in feces via bile, and that following oral administration of [carbonyl-^{14}C]-naldemedine to rats, the absorbed radioactivity is excreted mainly in feces via bile. The applicant explained that higher levels of radioactivity in urine observed with [oxadiazole-^{14}C]-naldemedine were considered attributed to urinary excretion of benzamidine, which is not traced by the radiolabel of [carbonyl-^{14}C]-naldemedine.

4.3.2 Excretion in milk in rats (CTD 4.2.2.5-05, Study ID S-297995-PF-239-N)

Following a single oral administration of [^{14}C]-naldemedine 1 mg/kg to lactating rats, concentrations of radioactivity in plasma and milk were determined. Radioactivity concentrations in plasma and milk peaked at 1 hour post-dose, and were below the LLOQ at 24 hours post-dose. The C_{max} and $AUC_{0\text{-}24h}$ of radioactivity in milk were 64.9% and 92.1% of those in plasma, respectively, showing that naldemedine was transferred into milk.

4.R Outline of the review conducted by PMDA

PMDA considers that there is no particular problem with the non-clinical pharmacokinetics of naldemedine.

5. Toxicity and Outline of the Review Conducted by PMDA

The following toxicity studies of naldemedine were conducted: single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other toxicity studies (dependence studies, toxicity studies on impurities, etc.). All doses and concentrations of naldemedine in the studies are expressed in terms of free base. Unless otherwise specified, 0.5% methylcellulose aqueous solution was used as vehicle.

5.1 Single-dose toxicity

5.1.1 Single oral dose toxicity study in rats (CTD 4.2.3.1-01, Study ID R-297995-TB-047-L)

Naldemedine 500 or 2000 mg/kg or vehicle was administered orally to male and female rats. There were no deaths in any group. At ≥500 mg/kg of naldemedine, reduced body weight gain was observed, which was reversible. The approximate lethal dose for a single oral dose of naldemedine in rats was determined to be >2000 mg/kg.

5.1.2 Single oral dose toxicity study in dogs (CTD 4.2.3.1-02, Study ID R-297995-TB-045-L)

Naldemedine 200 or 1000 mg/kg or vehicle was administered orally to male and female dogs. There were no deaths in any group. At ≥200 mg/kg of naldemedine, vomiting and increases in plasma ALP and total bilirubin were noted, but the vomiting resolved by 7 hours post-dose and the changes in plasma ALP and total bilirubin were reversible by 14 days post-dose. The approximate lethal dose for a single oral dose of naldemedine in dogs was determined to be >1000 mg/kg.

5.2 Repeated-dose toxicity

Oral toxicity studies were conducted in rats (1 and 6 months) and dogs (1, 3, and 9 months). The principal findings were reduced body weight gain in rats and hepatotoxicity (mild single cell necrosis in the liver accompanied by increases in plasma AST or ALT) in dogs. The reduced body weight gain observed in rats was considered due to antagonism of central opioid receptors by naldemedine because there is a report suggesting that opioid receptor antagonists reduce body weight gain by decreasing food intake (*AM J Physiol Regul Integr Comp Physiol*. 2003; 284: 1399-1408). The hepatocyte necrosis observed in dogs was considered due to direct hepatocellular injury. Exposures (AUCs) at the no-observed-adverse-effect levels (NOAELs) in rats (100 mg/kg/day [6 months]) and dogs (4 mg/kg/day [9 months]) were 3630 and 345 times, respectively, the human exposure at the proposed clinical dose (0.2 mg/day).

5.2.1 Rat 1-month oral toxicity study with a 1-month recovery period (CTD 4.2.3.2-01, Study ID R-297995-TB-048-L)

Naldemedine 30, 100, or 1000 mg/kg/day or vehicle was administered orally once daily for 1 month to male and female rats, and the 1000 mg/kg and vehicle control groups were given a 1-month recovery period. Decreases in body weight and food consumption were observed at ≥30 mg/kg, a decrease in plasma triglycerides at ≥100 mg/kg/day, and increases in liver and pituitary weights at 1000 mg/kg/day. Irregular estrous cycles (prolongation of diestrus) occurred in females at ≥30 mg/kg. All changes resolved following a recovery period.

Decreased food consumption and associated decrease in body weight were observed, but both findings were mild in severity; there were no clinical signs or hematology, clinical chemistry, or histopathological findings, etc. that would cause body weight changes. The decrease in plasma triglycerides was also associated with decreased food consumption. The increases in liver and pituitary weights were not associated with histopathological changes. Since these changes are considered of little toxicological significance, the NOAEL

was determined to be 1000 mg/kg/day. The irregular estrous cycles resolved during the dosing period in most animals, and there were no histopathological changes in the ovary, uterus, or mammary gland, etc. Thus, this finding was not considered to be significant general toxicity. The NOEL for irregular estrous cycles is described in Section 5.2.2, and a relevant reproductive toxicity study in Section 5.5.1.

5.2.2 Rat 1-month oral toxicity study (supplement) (CTD 4.2.3.2-02, Study ID R-297995-TB-091-L)

Since irregular estrous cycles were seen in females at ≥30 mg/kg in a rat 1-month oral toxicity study [see Section 5.2.1], naldemedine 0.3, 1, 3, or 10 mg/kg/day or vehicle was administered orally once daily for 1 month to female rats to investigate the effect of naldemedine on estrous cycles. Prolongation of diestrus occurred in all groups (1 of 10 animals, 3 of 10 animals, 1 of 10 animals, 4 of 10 animals, and 3 of 10 animals in the vehicle control, 0.3, 1, 3, and 10 mg/kg/day groups, respectively). The NOEL for irregular estrous cycles could not be determined.

5.2.3 Rat 6-month oral toxicity study with a 1-month recovery period (CTD 4.2.3.2-03, Study ID R-297995-TF-108-L)

Naldemedine 10, 100, or 1000 mg/kg/day or vehicle was administered orally once daily for 6 months to male and female rats, and the 1000 mg/kg and vehicle control groups were given a 1-month recovery period. Reduced body weight gain, increased plasma total cholesterol, etc. were noted at 1000 mg/kg, and all changes resolved following a recovery period. At 1000 mg/kg, body weight gain was reduced by >10% from the mid dosing period until the end of dosing. Soiled fur (suggestive of a decrease in grooming) was persistent until the end of dosing in many animals, suggesting the effects of reduced body weight gain. Thus, the NOAEL was determined to be 100 mg/kg/day.

5.2.4 Dog 1-month oral toxicity study with a 1-month recovery period (CTD 4.2.3.2-04, Study ID R-297995-TB-046-L)

Naldemedine 1, 3, 10, or 50 mg/kg/day or vehicle was administered orally once daily for 1 month to male and female dogs, and the 50 mg/kg and vehicle control groups were given a 1-month recovery period. The 50 mg/kg/day group showed vomiting or vomitus, increases in plasma ALT, ALP, and total cholesterol, and single cell necrosis in the liver associated with mild inflammatory cell infiltration. All changes resolved following a recovery period. Increases in plasma ALT, ALP, and total cholesterol were observed also at 3 and 10 mg/kg/day; these findings were not associated with histopathological changes, and were considered of no toxicological significance. The NOAEL was determined to be 10 mg/kg/day.

5.2.5 Dog 3-month oral toxicity study with a 1-month recovery period (CTD 4.2.3.2-05, Study ID S-297995-TF-109-L)

Naldemedine 1, 5, or 30 mg/kg/day or vehicle was administered orally once daily for 3 months to male and female dogs, and the 30 mg/kg and vehicle control groups were given a 1-month recovery period. At 30 mg/kg/day, vomitus, increases in plasma ALT, GGT, ALP, and total cholesterol, mild single cell necrosis in the liver, mild extramedullary hematopoiesis in the liver, atrophy of adipose tissue and deposition of gelatinous

material in the femoral bone marrow, and mild atrophy of pericardial and perirenal adipose tissues were observed. All changes resolved following a recovery period. The NOAEL was determined to be 5 mg/kg/day.

5.2.6 Dog 9-month oral toxicity study with a 1-month recovery period (CTD 4.2.3.2-06, Study ID S-297995-TF-219-L)

Naldemedine 1, 4, or 20 mg/kg or vehicle was administered orally once daily for 9 months to male and female dogs, and the 20 mg/kg and vehicle control groups were given a 1-month recovery period. The 20 mg/kg group showed increases in plasma ALT, GGT, ALP, and total cholesterol, mild single cell necrosis in the liver, and mild increases in Kupffer cells with brownish pigment deposition in the liver. All changes resolved following a recovery period. The NOAEL was determined to be 4 mg/kg/day.

5.3 Genotoxicity (CTD 4.2.3.3-01, 4.2.3.3-02, and 4.2.3.3-03, Study IDs R-297995-TB-051-L, R-297995-TF-052-L, and R-297995-TF-053-L)

Naldemedine was not genotoxic in a bacterial reverse mutation assay, a chromosomal aberration assay with cultured Chinese hamster lung cells, or a rat bone marrow micronucleus assay.

5.4 Carcinogenicity

Carcinogenicity studies were conducted in mice and rats; neither study showed any carcinogenic potential of naldemedine. Exposures (AUCs) at a dose of 100 mg/kg/day (at which no tumors were observed in mice or rats) in mice and rats were 17,532 and 6316 times, respectively, the human exposure at the proposed clinical dose (0.2 mg/day).

5.4.1 Two-year oral carcinogenicity study in mice (CTD 4.2.3.4-01, Study ID S–297995–TF–265–L)

Naldemedine 10, 30, or 100 mg/kg/day or vehicle was administered orally once daily for 2 years to male and female mice. As a result, there were no naldemedine-related neoplastic or non-neoplastic findings, and naldemedine was not carcinogenic in mice.

5.4.2 Two-year oral carcinogenicity study in rats (CTD 4.2.3.4-02, Study ID S–297995–TF–266–L)

Naldemedine 10, 30, or 100 mg/kg/day or vehicle was administered orally once daily for 2 years to male and female rats. As a result, there were no naldemedine-related neoplastic or non-neoplastic findings, and naldemedine was not carcinogenic in rats.

5.5 Reproductive and developmental toxicity

The following reproductive and developmental toxicity studies were conducted: a rat study of fertility and early embryonic development to implantation, embryo-fetal development studies in rats and rabbits, and a rat study for effects on pre- and postnatal development, including maternal function. Exposures (AUCs) at the NOAELs for fertility or embryo-fetal development (1000 mg/kg/day in rats, 100 mg/kg/day in rabbits) in rats and rabbits were 23,081 and 226 times, respectively, the human exposure at the proposed clinical dose (0.2 mg/day). It has been suggested that naldemedine crosses the placenta and is excreted in milk [see Sections 4.2.2 and 4.4.2].

5.5.1 Rat study of fertility and early embryonic development to implantation (CTD 4.2.3.5-01, Study ID S-297995-TF-104-L)

Naldemedine 1, 10, 100, or 1000 mg/kg/day or vehicle was administered orally to male and female rats once daily (from 28 days prior to mating until the day before necropsy for males; and from 14 days prior to mating until gestation day 7 for females). In males, decreases in body weight and food consumption were observed at ≥10 mg/kg/day. Females given ≥10 mg/kg/day showed irregular estrous cycles (decreased frequency of estrus). Females given 1000 mg/kg/day showed decreases in body weight gain and food consumption during early dosing period and early gestation. Irregular estrous cycles occurred in 5 of 20 females given 10 mg/kg/day, in 12 of 20 females given 100 mg/kg/day, and in 13 of 20 females given 1000 mg/kg/day. However, all of these females had estrus during the pre-mating or mating period and successfully copulated with males during the mating period except for 1 female in the 1000 mg/kg/day group. There were no effects on embryo-fetal development. The NOAEL for parental general toxicity was determined to be 1 mg/kg/day in males and 100 mg/kg/day in females. The NOAEL for reproductive toxicity was determined to be 1000 mg/kg/day in males and 1 mg/kg/day in females. The NOAEL for embryonic development was determined to be 1000 mg/kg/day.

5.5.2 Embryo-fetal development study in rats (CTD 4.2.3.5-02, Study ID S-297995-TF-146-L)

Naldemedine 10, 100, or 1000 mg/kg/day or vehicle was administered orally to pregnant rats once daily from gestation day 7 to 17. In dams, decreases in body weight gain and food consumption were observed during early dosing period at ≥10 mg/kg. There were no effects on embryo-fetal development. The NOAEL for maternal general toxicity was determined to be <10 mg/kg/day. The NOAELs for maternal reproductive toxicity and embryo-fetal development were determined to be 1000 mg/kg/day.

5.5.3 Embryo-fetal development study in rabbits (CTD 4.2.3.5-03, Study ID S-297995-TF-182-L)

Naldemedine 25, 100, or 400 mg/kg/day or vehicle was administered orally to pregnant rabbits once daily from gestation day 6 to 18. At 400 mg/kg/day, 2 of 19 females aborted on gestation days 21 and 22, and 1 of 19 females delivered prematurely on gestation day 27. The applicant explained that the abortion and premature delivery were attributable to naldemedine-related marked decreases in food consumption. Dams given ≥25 mg/kg/day showed decreases in body weight gain and food consumption. Dams given 400 mg/kg/day showed decreased body weight and decreased fecal volume. In fetuses, decreased fetal body weights and decreased placental weights were observed at 400 mg/kg/day. The NOAEL for maternal general toxicity was determined to be <25 mg/kg/day and the NOAELs for maternal reproductive toxicity and embryo-fetal development were determined to be 100 mg/kg/day.

5.5.4 Rat study for effects on pre- and postnatal development, including maternal function (CTD 4.2.3.5-04, Study ID S-297995-TF-275-L)

Naldemedine 1, 30, or 1000 mg/kg/day or vehicle was administered orally to pregnant rats once daily from gestation day 7 to lactation day 20. At 1000 mg/kg, 1 of 22 dams died at parturition on gestation day 22. Although the cause of death could not be identified, as there were no effects on clinical observations or body

weight, etc., the applicant explained that the death was unlikely to be related to naldemedine. Dams given ≥30 mg/kg/day showed decreases in body weight gain and food consumption during gestation. On lactation days 0 to 4, 5 of 22 dams given 30 mg/kg/day and 3 of 22 dams given 1000 mg/kg/day had total litter loss, probably due to poor nursing. F_1 pups in the ≥30 mg/kg/day groups showed an increase in the number of dead pups, decreased birth index, and a decrease in viability index on lactation day 4. F_1 pups in the 1000 mg/kg/day group showed decreased body weights prior to weaning and delayed pinna unfolding. The applicant explained that the findings in pups were attributable to a deterioration in clinical signs in dams due to decreases in food consumption and body weight, and due to associated poor nursing. The NOAELs for maternal general and reproductive toxicity and F1 developmental toxicity were determined to be 1 mg/kg/day.

5.6 Other toxicity studies

5.6.1 Dependence studies

5.6.1.1 Drug discrimination study in rats (CTD 4.2.3.7-15, Study ID S-297995-TF-334-L)

Male rats were trained to discriminate morphine hydrochloride from saline and then given a single oral dose of naldemedine 0.03, 0.1, or 0.3 mg/kg/day. As a result, naldemedine at all dose levels produced no morphine hydrochloride-like discriminative stimulus effects.

5.6.1.2 Intravenous self-administration study in monkeys (CTD 4.2.3.7-16, Study ID S-297995-TF-335-L)

Male and female monkeys were trained to self-administer intravenous cocaine, pentazocine, codeine phosphate, and/or pentobarbital and then allowed to self-administer intravenous naldemedine 0.03, 0.1, 0.3, 1, 3, or 10 μg/kg or vehicle (2.5% DMSO/10% polyethyleneglycol 400/saline solution) over a 2-hour daily session for 4 days. As a result, the number of self-administrations was similar in both the naldemedine and vehicle control groups. Male and female monkeys were trained in the same manner and then allowed to self-administer intravenous naldemedine 1, 3, or 10 μg/kg or vehicle over a 24-hour daily session for 2 to 3 weeks to evaluate the reinforcing effect of naldemedine. As a result, the number of self-administrations was similar in both the naldemedine and vehicle control groups. Based on the above, naldemedine was considered to have no reinforcing effect.

5.6.1.3 Physical dependence study in rats (CTD 4.2.3.7-17, Study ID S-297995-TF-333-L)

Naldemedine 30 or 100 mg/kg or vehicle was administered orally to male rats twice daily for 28 days, and then the animals were observed for withdrawal symptoms during the 7-day withdrawal period. Decreased food consumption or a trend towards decrease in food consumption and reduced body weight gain were observed during the dosing period at 30 and 100 mg/kg, but there were no naldemedine-related changes in clinical observations. Increased muscle tone was noted on Days 1 to 4 of the withdrawal period, but there were no typical withdrawal symptoms of drugs producing physical dependence (i.e., transient decrease in body weight, reduced body weight gain, decreased food consumption, other changes in clinical observations) during the withdrawal period. Thus, the increased muscle tone was not considered a withdrawal symptom suggestive of physical dependence. Based on the above, naldemedine was considered to produce no physical dependence.

5.6.1.4 Ability of naldemedine to precipitate morphine withdrawal in morphine-dependent mice (CTD 4.2.3.7-21, Study ID R-297995-EB-073-N)

Male mice were made physically dependent on morphine by subcutaneous administration of morphine 5 times daily for 4 consecutive days, and then given a single oral dose of naldemedine 0.01, 0.1, 1, or 10 mg/kg or vehicle, to assess the ability of naldemedine to precipitate morphine withdrawal. The frequency of diarrhea (a peripherally-mediated morphine withdrawal symptom) increased at doses of 1 and 10 mg/kg naldemedine. Based on the above, naldemedine at ≥1 mg/kg was considered to precipitate peripherally-mediated morphine withdrawal symptoms.

5.6.1.5 Ability of naldemedine to precipitate morphine withdrawal in morphine-dependent rats (CTD 4.2.3.7-22, Study ID S-297995-SB-270-N)

Male rats were made physically dependent on morphine by continuous subcutaneous administration of morphine for 5 days, and then given a single oral dose of naldemedine 0.01, 0.03, 0.1, 0.3, 1, or 3 mg/kg or vehicle, to assess the ability of naldemedine to precipitate morphine withdrawal. Decreased body weight was observed at ≥0.3 mg/kg, increases in the score of diarrhea at ≥1 mg/kg, and an increase in the score of teeth chattering at 3 mg/kg. Based on the above, naldemedine was considered to precipitate peripherally-mediated morphine withdrawal symptoms at ≥0.3 mg/kg and centrally-mediated morphine withdrawal symptoms at ≥3 mg/kg.

5.6.2 Immunotoxicity study in rats (CTD 4.2.3.7-01, Study ID S-297995-TB-234-L)

Naldemedine 30, 100, or 1000 mg/kg/day or vehicle was administered orally to male and female rats once daily for 1 month to assess the effect of naldemedine on T-cell dependent antibody responses. Although there were transient decreases in body weight at all dose levels, naldemedine had no effects on the anti-keyhole-limpet hemocyanin antibody titer. Thus, naldemedine was not considered to have any effects on T-cell dependent antibody formation.

5.6.3 Effects on reproductive hormones

5.6.3.1 Effects on estrous cycle and plasma reproductive hormone concentrations in rats (CTD 4.2.3.7-07 [Reference data], Study ID R-297995-TF-105-R)

Naldemedine 1000 mg/kg/day or vehicle was administered orally to female rats once daily for 16 days to investigate the effects of naldemedine on estrous cycle and plasma reproductive hormone concentrations. Irregular estrous cycles (decreased frequency of estrus and prolongation of diestrus) and increases in plasma prolactin and progesterone levels were observed at 1000 mg/kg/day.

5.6.3.2 Effects on plasma prolactin concentrations in rats (CTD 4.2.3.7-06 [Reference data], Study ID S-297995-TF-162-N)

A single oral dose of naldemedine 1, 10, 100, or 1000 mg/kg or vehicle was administered to male and female rats, to investigate the effects of naldemedine on plasma prolactin concentrations. No males showed changes

in prolactin concentrations in any group. In females, prolactin levels at 8 hours post-dose were higher at ≥10 mg/kg, but the extent of the increase was almost comparable across the dose groups.

5.6.4 Bacterial reverse mutation assays for impurities (CTD 4.2.3.7-02, 4.2.3.7-03, and 4.2.3.7-04, Study IDs S-297995-TB-305-L, S-297995-TB-319-L, and S-297995-TB-320-L)

Bacterial reverse mutation assays were conducted for potential impurities likely to occur during the manufacturing process (Impurity C, Impurity B, Impurity A). As a result, none of the impurities were mutagenic.

5.6.5 Skin phototoxicity study in hairless mice (CTD 4.2.3.7-05, Study ID S-297995-TB-249-L)

Female hairless mice received a single oral dose of naldemedine 30 or 300 mg/kg or vehicle and were then exposed to UV irradiation (UV dose, 10 J/cm^2; wavelength range, 290-400 nm), to evaluate the skin phototoxicity of naldemedine. No skin reactions following UV exposure were observed in any group, and naldemedine was considered to have no phototoxic potential.

5.R Outline of the review conducted by PMDA

5.R.1 Withdrawal symptoms

Naldemedine precipitated peripherally- and centrally-mediated morphine withdrawal symptoms in morphine-dependent rats [see Section 5.6.1.5]. PMDA asked the applicant to discuss whether naldemedine has the potential to precipitate morphine withdrawal in clinical use.

The applicant's response:

The results of a study in morphine-dependent rats indicated that naldemedine precipitates peripherally-mediated morphine withdrawal symptoms at ≥0.3 mg/kg and centrally-mediated morphine withdrawal symptoms at ≥3 mg/kg. As coadministration of morphine hydrochloride has little effect on plasma naldemedine concentrations, the C_{max} values following single oral doses of 0.1 and 1 mg/kg of naldemedine in morphine-dependent rats are estimated to be 6.3 and 37.9 ng/mL, respectively. Since these values (6.3 and 37.9 ng/mL) are 3.2 and 19 times, respectively, the C_{max} (2 ng/mL) in humans at the proposed clinical dose (0.2 mg/day), naldemedine is unlikely to precipitate centrally-mediated morphine withdrawal symptoms in clinical use. However, the possibility of precipitating peripherally-mediated morphine withdrawal symptoms cannot be ruled out.

Since naldemedine may precipitate peripherally-mediated opioid withdrawal symptoms in clinical use, PMDA continues to discuss the risk of opioid withdrawal syndrome induced by naldemedine in Section 7.R.2.4.4.

5.R.2 Irregular estrous cycles in rats

PMDA asked the applicant to discuss whether irregular estrous cycles observed in rats are relevant to humans.

The applicant's explanation:

Irregular estrous cycles were observed in a rat 1-month oral toxicity study [see Section 5.2.1] and a supplemental study [see Section 5.2.2] and a rat study of fertility and early embryonic development to implantation [see Section 5.5.1]. In all studies, the estrous cycle was recovered during the dosing period in most animals. In the rat study of fertility and early embryonic development to implantation, almost all females successfully copulated with males. Thus, these findings are considered minor effects that do not interfere with the reproductive function.

In studies that investigated the effects of naldemedine on plasma prolactin concentrations in female rats [see Sections 5.6.3.1 and 5.6.3.2], plasma prolactin levels were increased. Rats have a very short estrous cycle and elevated concentrations of prolactin induce prolonged luteal phase (*The physiology of reproduction*. *Raven Press.*1988;1893-1919). In humans, however, the luteal phase is maintained physiologically for a prolonged period, regardless of prolactin levels (*The physiology of reproduction. Raven Press*: 1988; 1971-1994). Thus, the luteal phase in humans should be regulated differently from that in rats. The C_{max} and AUC at the 1 mg/kg dose of naldemedine in rats (at which no plasma prolactin changes occurred) were 0.1 μg/mL and 0.2 μg·h/mL, respectively. These values were 50 and 12 times, respectively, the human exposures ($C_{max,}$ 2 ng/mL; AUC, 16.9 ng·h/mL) at the proposed clinical oral dose (0.2 mg/day). Hence, the transient increases in prolactin levels and associated irregular estrous cycles observed in rats are considered of little relevance to humans.

PMDA accepted the applicant's explanation.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

An oral solution and an oral suspension were used in a Japanese phase I single-dose study (Study V9211), an oral solution of [^{14}C]-naldemedine in a foreign mass balance study (Study V9215), and an immediate-release tablet in other studies. An immediate-release tablet (identical to the to-be-marketed formulation with different strength) was used in Japanese phase III studies (Studies V9236 to V9239), foreign phase I studies (V921A to V921E), and foreign phase III studies (V9231, V9232, V9235).

Plasma and urine concentrations of unchanged naldemedine and its metabolites (nor-naldemedine, naldemedine 3-G, benzamidine) were determined by LC-MS/MS. The LLOQ for unchanged naldemedine in plasma was 0.01 ng/mL in all studies. The LLOQ for nor-naldemedine or naldemedine 3-G in plasma was 0.12 ng/mL in the mass balance study (Study V9215) and a foreign single-dose study of naldemedine in subjects receiving morphine sulfate (Study V9216), 0.08 ng/mL in a foreign phase II study in patients with chronic non-cancer pain (Study V9221), and 0.04 ng/mL in other studies. The LLOQ for benzamidine in plasma was 1.20 ng/mL in the mass balance study (Study V9215) and 0.30 ng/mL in other studies. The LLOQ for unchanged naldemedine in urine was 0.10 ng/mL. The LLOQ for nor-naldemedine in urine was 0.40 ng/mL in Japanese phase I single-dose and multiple-dose studies (Studies V9211 and V9213) and 1.20 ng/mL in the mass balance study (Study V9215). The LLOQ for benzamidine in urine was 3.00 ng/mL in the Japanese phase I single-dose study (Study V9211), 0.30 ng/mL in the Japanese phase I multiple-dose study (Study V9213), and 1.20 ng/mL

in the mass balance study (Study V9215). Plasma concentrations of morphine hydrochloride and its metabolites (morphine 3-G and morphine 6-G) were determined by LC-MS/MS, and the LLOQs were 0.50 ng/mL, 10.0 ng/mL, and 2.00 ng/mL, respectively.

6.1.1 Foreign phase I study (Food effect) (CTD 5.3.1.2-01, Study ID 1311V921A [[redacted] to [redacted]], "Study V921A")

A randomized, open-label, crossover study was conducted at 1 site overseas, to evaluate the effect of food on the pharmacokinetics and safety of naldemedine of a single oral dose of 0.2 mg naldemedine (the to-be-marketed formulation) in non-Japanese healthy adults between 18 and 50 years of age (N = 18).

A single oral dose of 0.2 mg of naldemedine was administered under fasted or fed conditions (30 minutes after a high-fat breakfast), and a ≥13-day washout period was included between the periods.

All 18 randomized subjects were included in the pharmacokinetic and safety analysis populations. Pharmacokinetic results are shown in Table 17.

Table 17. Plasma pharmacokinetic parameters of unchanged naldemedine following administration of naldemedine 0.2 mg under fasted or fed conditions

	n[a)]	C_{max} (ng/mL)	t_{max} (h)[b)]	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)
Fasted	**15**	**3.07 (18.7)**	**0.75 (0.50, 2.00)**	**23.79[c)] (17.1)**	**10.9[c)] (14.3)**
Fed	**18**	**2.01 (19.0)**	**2.50 (0.75, 5.02)**	**23.13 (14.0)**	**10.9 (17.9)**

Geometric mean (% coefficient of variation [CV])
a) No. of subjects with drug concentration measurements, b) Median (Minimum, Maximum), c) n = 14

The geometric mean ratios (fed/fasted) of C_{max} and $AUC_{0\text{-}inf}$ [two-sided 90% confidence interval (CI)] were 0.65 [0.58, 0.72] and 0.97 [0.93, 1.01], respectively.

Adverse events occurred in 33.3% (5 of 15) of subjects treated under fasted conditions and 27.8% (5 of 18) of subjects treated under fed conditions. Adverse events occurring in ≥2 subjects treated under fasted or fed conditions were ear pain (13.3% [2 of 15] of fasted subjects, 0.0% [0 of 18] of fed subjects), nausea (0.0% [0 of 15] of fasted subjects, 11.1% [2 of 18] of fed subjects) and headache (0.0% [0 of 15] of fasted subjects, 16.7% [3 of 18] of fed subjects). No adverse drug reactions occurred in fasted subjects. Adverse drug reactions occurred in 16.7% (3 of 18) of fed subjects. Of these, headache (16.7% [3 of 18 subjects]) and nausea (11.1% [2 of 18 subjects]) were reported by ≥2 subjects. There were no deaths or serious adverse events. No adverse events led to treatment discontinuation in fasted subjects. The incidence of adverse events leading to treatment discontinuation in fed subjects was 5.6% (1 of 18 subjects) (feeling hot), but the event was mild in severity and its causal relationship to study drug was ruled out.

6.1.2 Studies using human biomaterials

6.1.2.1 Serum protein binding and distribution in blood cells (CTD 5.3.2.1-01 and 5.3.2.1-02, Study IDs R-297995-PB-024-N and R-297995-PB-023-N)

When [^{14}C]-naldemedine 0.02, 0.2, or 2 μg/mL was added to human serum, the serum protein binding (the mean at each concentration) was 93.2% to 94.2%, showing no concentration-dependence over the range tested.

When [^{14}C]-naldemedine 0.02, 0.2, or 2 μg/mL was added to 4% human serum albumin solution, 0.08% α_1-acid glycoprotein solution, and 1% γ-globulin solution, the serum protein binding (the mean) was 95.3% to 96.0%, 22.7% to 25.9%, and 17.2% to 19.5%, respectively.

When [^{14}C]-naldemedine 0.02, 0.2, or 2 μg/mL was added to human blood, the distribution in blood cells (the mean at each concentration) was 13.5% to 16.3%, showing no concentration-dependence over the range tested.

6.1.2.2 Studies on *in vitro* metabolites (CTD 5.3.2.2-01 and 4.2.2.4-01, Study IDs R-297995-PB-063-N and S-297995-PF-200-N)

Metabolism of [oxadiazole-^{14}C]-naldemedine was studied using cryopreserved human hepatocytes. The major metabolites were nor-naldemedine, naldemedine 3-G, and naldemedine 6-G, accounting for 6% to 7%, 3%, and 3%, respectively, of the radioactivity in the sample. Benzamidine was not formed.

Using human liver microsomes, CYP isozyme selective inhibitors, recombinant human CYP isozymes, and UGT enzymes, CYP isozymes responsible for metabolism of [carbonyl-^{14}C]-naldemedine were identified. The results indicated that the formation of nor-naldemedine from naldemedine is predominantly mediated by CYP3A4 and that the formation of naldemedine 3-G and naldemedine 6-G from naldemedine is predominantly mediated by UGT1A3.

6.1.2.3 Inhibition of human liver drug metabolizing enzymes by naldemedine and its metabolite (CTD 5.3.2.2-02 and 5.3.2.2-03, Study IDs R-297995-PF-064-N and S-297995-PB-338-N)

Human liver microsomes were used to investigate whether naldemedine (0.03-20 μmol/L) and its metabolite nor-naldemedine (1 and 20 nmol/L) inhibit CYP isozymes [5)] (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, CYP4A11). Naldemedine or its metabolite, nor-naldemedine, did not inhibit any of the CYP isozymes over the concentration range tested.

6.1.2.4 Induction of human liver drug metabolizing enzymes by naldemedine (CTD 5.3.2.2-04 and 5.3.2.2-05, Study IDs S-297995-PF-176-N and S-297995-PF-298-N)

Human hepatocytes were used to investigate whether naldemedine (1-10 μmol/L) induces CYP1A2, CYP3A4, UGT1A2, UGT1A6, and UGT2B7. Naldemedine at up to 10 μmol/L did not induce CYP1A2, UGT1A6, or UGT2B7. Naldemedine at up to 1 μmol/L did not induce CYP3A4/5. While naldemedine at ≥1 μmol/L induced UGT1A2, marker activity[6)] was increased by 10% to 30%. Since 1 μmol/L (743 ng/mL of naldemedine) is higher than the C_{max} (2 ng/mL) of naldemedine at the proposed clinical dose (0.2 mg/day) [see Sections 6.2.8 and 6.2.9], the applicant explained that naldemedine is unlikely to induce any enzyme in clinical use.

[5)] Naldemedine only was tested for CYP2A6, CYP2E1, and CYP4A11. For CYP3A4/5, naldemedine was tested using 4 substrates (testosterone, midazolam, nifedipine, atorvastatin), and nor-naldemedine was tested using 2 substrates (testosterone, midazolam).

[6)] The following enzyme activities were used as markers: phenacetin *O*-deethylase for CYP1A2 activity, testosterone 6β-hydroxylase for CYP3A4 activity, estradiol 3-glucuronidase for UGT1A2 activity, acetaminophen *O*-glucuronidase for UGT1A6 activity, and morphine 3- glucuronidase for UGT2B7 activity

Human hepatocytes were used to investigate whether naldemedine (0.03-10 μmol/L) induces CYP2B6. Naldemedine caused up to an 82% increase in CYP2B6 mRNA levels and up to a 197% increase in CYP2B6 marker activity.[7)] These values were <20% of increases caused by positive control, phenobarbital. The applicant explained that naldemedine is unlikely to induce CYP2B6 in clinical use.

6.1.2.5 Studies on P-gp-mediated transport (CTD 4.2.2.6-01 and 4.2.2.6-04, Study IDs R-297995-PF-067-N and S-297995-PF-340-N)

[^{14}C]-naldemedine 0.2 μmol/L was added to Caco-2 cells to evaluate P-gp-mediated transport of naldemedine. As a result, naldemedine was shown to be a P-gp substrate. While naldemedine is a P-gp substrate and has very low ability to cross the blood-brain barrier, it may precipitate opioid withdrawal syndrome or reduce opioid analgesia in patients with a compromised blood-brain barrier. Thus, the applicant explained that a relevant precautionary statement will be included in the package insert.

P-gp inhibition by naldemedine (5 μmol/L) and nor-naldemedine (1 and 20 μmol/L) was investigated using [^{3}H]-digoxin (the known P-gp substrate). As a result, naldemedine or nor-naldemedine was not a P-gp inhibitor.

6.1.2.6 Studies on OATP1B1-, OATP1B3-, OCT1-, OCT2-, OAT1-, OAT3-, and BCRP-mediated transport (CTD 4.2.2.6-02 to 4.2.2.6-04, Study IDs S-297995-PF-285-N, S-297995-PF-297-N, and S-297995-PF-340-N)

In order to determine whether naldemedine is a substrate for OATP1B1, OATP1B3, OCT1, OAT1, OAT3, OCT2, and BCRP, the transport of naldemedine (0.5 and 2 μmol/L [0.5-10 μmol/L for BCRP only]) was investigated using transporter-transfected cells and BCRP knockdown cells. Naldemedine was not considered a substrate for these transporters.

In order to determine whether naldemedine and its metabolite, nor-naldemedine, inhibit OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, and BCRP, the effects of naldemedine (1 and 5 μmol/L [5 μmol/L for BCRP only]) and nor-naldemedine (1 and 20 nmol/L) on the transport of standard substrates[8)] were investigated using transporter-transfected cells. Naldemedine inhibited OCT2- and OAT3-mediated substrate transport by 30% and 41%, respectively, and the activities of other transporters by <15%. Its metabolite, nor-naldemedine, inhibited OCT1-mediated substrate transport by 38% and the activities of other transporters by <10%. Based on the above, the applicant explained that naldemedine and nor-naldemedine are unlikely to inhibit these transporters in clinical use of naldemedine.

6.2 Clinical pharmacology

6.2.1 Japanese phase I single-dose study (CTD 5.3.3.1-01, Study ID 0824V9211 [[redacted] to [redacted]], "Study V9211")

A placebo-controlled, randomized, double-blind, parallel-group study was conducted at 1 site in Japan to

7) Bupropion hydroxylase activity was used as a marker.

8) For evaluation of naldemedine, the following substrates were used as standard substrates: estrone-3-sulfate for OATP1B1 and OAT3, fluo-3 for OATP1B3, metformin for OCT1 and OCT2, p-aminohippuric acid for OAT1, and prazosin for BCRP.
For evaluation of nor-naldemedine, the following substrates were used as standard substrates: estradiol-17-β-D-glucuronide for OATP1B1 and OATP1B3, metformin for OCT1 and OCT2, p-aminohippuric acid for OAT1, and estrone-3-sulfate for OAT3 and BCRP

evaluate the safety and pharmacokinetics of a single oral dose of naldemedine in Japanese healthy adult men aged ≥20 and <40 years (target sample size, 56 subjects [6 on naldemedine and 2 on placebo at each dose level).

A single oral dose of placebo or naldemedine 0.1, 0.3, 1, 3, 10, 30, or 100 mg was administered under fasted conditions.

All 56 randomized subjects (14 on placebo, 42 on naldemedine) were included in the safety analysis population, and all of 42 subjects treated with naldemedine were included in the pharmacokinetic analysis population.

The incidences of adverse events were 14.3% (2 of 14 subjects) in the placebo group, 33.3% (2 of 6 subjects) in the naldemedine 0.1 mg group, 33.3% (2 of 6 subjects) in the naldemedine 3 mg group, 33.3% (2 of 6 subjects) in the naldemedine 10 mg group, 16.7% (1 of 6 subjects) in the naldemedine 30 mg group, and 33.3% (2 of 6 subjects) in the naldemedine 100 mg group. The incidences of adverse drug reactions were 7.1% (1 of 14 subjects) in the placebo group, 33.3% (2 of 6 subjects) in the naldemedine 0.1 mg group, 33.3% (2 of 6 subjects) in the naldemedine 10 mg group, 16.7% (1 of 6 subjects) in the naldemedine 30 mg group, and 33.3% (2 of 6 subjects) in the naldemedine 100 mg group. No adverse events or adverse drug reactions occurred in ≥2 subjects in any group. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

The plasma pharmacokinetic parameters of unchanged naldemedine and its metabolites are shown in Table 18. The $AUC_{0\text{-}inf}$ and C_{max} of unchanged naldemedine increased in an almost dose-proportional manner. The $AUC_{0\text{-}inf}$ of the major metabolite, nor-naldemedine, was 20% to 29% of the parent drug $AUC_{0\text{-}inf}$, and no dose-dependency was observed. Among its metabolites, benzamidine was not detected in plasma at doses up to 3 mg.

The geometric mean urinary excretion was almost constant regardless of dose level: unchanged naldemedine, 15.9% to 23.1%; nor-naldemedine, 0.2% to 0.4%; and naldemedine 3-G, 0.3% to 0.4%. The urinary excretion of benzamidine was below the LLOQ at 0.1 mg and 7.4% to 12.7% at 0.3 to 100 mg, which was almost constant regardless of dose.

Table 18. Plasma pharmacokinetic parameters of unchanged naldemedine and its metabolites following a single oral dose of naldemedine

Naldemedine dose	Compound	C_{max} (ng/mL)	t_{max}[a)] (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)
0.1 mg	Unchanged naldemedine	1.98 (30.9)	0.5 (0.5, 1.0)	11.60 (25.4)	8.3 (9.8)
	Nor-naldemedine	0.09 (21.2)	3.5 (3.0, 5.0)	2.51 (43.9)	21.1 (35.0)
	Naldemedine 3-G	0.09 (NC)	2.8 (1.5, 4.0)	NC	NC
0.3 mg	Unchanged naldemedine	4.47 (19.3)	0.5 (0.3, 0.5)	32.53 (16.5)	9.2 (20.4)
	Nor-naldemedine	0.18 (42.0)	4.0 (3.0, 5.0)	5.94 (17.7)	23.2 (42.6)
	Naldemedine 3-G	0.08 (35.0)	1.8 (1.0, 3.0)	0.84 (27.7)	6.4 (50.8)
1 mg	Unchanged naldemedine	16.2 (23.0)	0.5 (0.5, 1.0)	107.7 (7.9)	7.6 (10.9)
	Nor-naldemedine	0.83 (34.3)	4.8 (3.5, 5.0)	21.39 (30.5)	16.6 (12.9)
	Naldemedine 3-G	0.32 (38.5)	2.5 (1.5, 4.5)	3.13 (56.8)	6.1 (28.2)
3 mg	Unchanged naldemedine	52.2 (14.3)	0.5 (0.3, 1.5)	320.8 (15.3)	8.1 (14.6)
	Nor-naldemedine	2.47 (33.7)	5.0 (3.5, 5.0)	82.96 (23.3)	26.9 (26.7)
	Naldemedine 3-G	0.85 (33.3)	2.8 (1.0, 5.0)	8.12 (21.2)	6.7 (10.0)
10 mg	Unchanged naldemedine	217 (26.3)	0.5 (0.5, 1.0)	1135 (17.9)	6.6 (6.8)
	Nor-naldemedine	9.74 (16.1)	4.0 (2.5, 5.0)	223.6 (23.3)	13.6 (15.3)
	Naldemedine 3-G	2.86 (31.0)	1.8 (1.0, 3.0)	25.53 (25.5)	6.7 (8.6)
30 mg	Unchanged naldemedine	822 (39.8)	0.5 (0.5, 1.0)	3969 (24.6)	6.1 (5.2)
	Nor-naldemedine	36.5 (26.3)	4.0 (3.0, 5.0)	842.5 (37.3)	14.6 (11.9)
	Naldemedine 3-G	11.5 (45.7)	2.8 (1.5, 5.0)	104.9 (51.7)	5.5 (7.8)
100 mg	Unchanged naldemedine	2510 (23.7)	0.5 (0.5, 0.5)	13410 (16.0)	5.2 (3.9)
	Nor-naldemedine	162 (17.5)	4.8 (4.5, 5.0)	3044 (22.6)	11.1 (10.4)
	Naldemedine 3-G	41.5 (31.0)	3.5 (1.5, 5.0)	335.4 (35.6)	4.7 (4.7)

n = 6, Geometric mean (% geometric CV); a) Median (Minimum, Maximum); NC, not calculated

6.2.2 Japanese phase I multiple-dose study (CTD 5.3.3.1-02, Study ID 0917V9213 [[redacted] 20[redacted] to [redacted] 20[redacted]], "Study V9213")

A placebo-controlled, randomized, double-blind, parallel-group study was conducted at 1 site in Japan to evaluate the safety and pharmacokinetics of multiple oral doses of naldemedine in Japanese healthy adult men aged ≥20 and <40 years (target sample size, 36 subjects [3 on placebo and 9 on naldemedine at each dose level).

Placebo or naldemedine 3, 10, or 30 mg was administered orally once daily under fasted conditions for 10 days.

All 36 randomized subjects (9 on placebo, 27 on naldemedine) were included in the safety analysis population, and all of 27 subjects treated with naldemedine were included in the pharmacokinetic analysis population.

The incidences of adverse events were 33.3% (3 of 9 subjects) in the placebo group, 33.3% (3 of 9 subjects) in the naldemedine 3 mg group, 33.3% (3 of 9 subjects) in the naldemedine 10 mg group, and 33.3% (3 of 9 subjects) in the naldemedine 30 mg group. The incidences of adverse drug reactions were 11.1% (1 of 9 subjects) in the placebo group, 22.2% (2 of 9 subjects) in the naldemedine 3 mg group, 11.1% (1 of 9 subjects) in the naldemedine 10 mg group, and 22.2% (2 of 9 subjects) in the naldemedine 30 mg group. Adverse events occurring in ≥2 subjects in any group were diarrhoea (0% [0 of 9 subjects] in the placebo group, 22.2% [2 of 9 subjects] in the naldemedine 3 mg group, 11.1% [1 of 9 subjects] in the naldemedine 10 mg group, 11.1% [1

of 9 subjects] in the naldemedine 30 mg group), and the events of diarrhoea occurring in naldemedine-treated subjects were all classified as adverse drug reactions. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

Table 19 shows the plasma pharmacokinetic parameters of unchanged naldemedine and its metabolites. Plasma concentrations of unchanged naldemedine reached a steady-state within 2 days, and the $AUC_{0-\tau}$ and C_{max} increased in an almost dose-proportional manner. The median t_{max} was 0.50 to 0.75 hours at all dose levels, and multiple dosing had no effect on it. The $AUC_{0-\tau}$ of the major metabolite, nor-naldemedine, was approximately 20% of the parent drug $AUC_{0-\tau}$ on Day 10. The geometric mean urinary excretion was 15.3% to 19.7% for unchanged naldemedine, 0.2% to 0.5% for nor-naldemedine, and 0.4% to 0.5% for naldemedine 3-G. Multiple dosing had no effect on the geometric mean urinary excretion. The geometric mean urinary excretion of benzamidine (the primary metabolite in urine) was 7.77% to 8.71% on Day 1 and 22.1% to 27.6% on Day 10.

Table 19. Plasma pharmacokinetic parameters of unchanged naldemedine and its metabolites following multiple oral doses of naldemedine

Naldemedine dose		Compound	C_{max} (ng/mL)	t_{max} [a] (h)	$AUC_{0-\tau}$ (ng·h/mL)	$t_{1/2}$ (h)
3 mg	Day 1	Unchanged naldemedine	56.8 (29.3)	0.8 (0.3, 1.5)	343.7 (13.5)	—
		Nor-naldemedine	2.21 (30.7)	4.0 (4.0, 6.0)	36.19 (29.4)	—
		Naldemedine 3-G	0.99 (41.6)	1.5 (1.0, 4.0)	9.16 (31.3)	—
		Benzamidine	NC	NC [b]	NC [b]	—
	Day 10	Unchanged naldemedine	73.8 (27.1)	0.5 (0.5, 1.0)	407.5 (16.8)	37.8 (27.8)
		Nor-naldemedine	4.21 (18.5)	4.0 (2.5, 5.0)	67.22 (22.3)	79.5 (27.4)
		Naldemedine 3-G	0.89 (37.6)	2.0 (1.0, 3.0)	8.64 (31.8)	7.2 (15.7)
		Benzamidine	0.33 (7.1)	12 (6.0, 12) [c]	2.66 (80.3) [c]	NC [b]
10 mg	Day 1	Unchanged naldemedine	177 (24.6)	0.8 (0.5, 4.0)	1094 (21.5)	—
		Nor-naldemedine	10.5 (32.4)	4.0 (4.0, 12)	156.2 (25.1)	—
		Naldemedine 3-G	4.31 (26.3)	3.0 (1.5, 5.0)	33.90 (26.8)	—
		Benzamidine	0.48 (23.1)	12 (8.0, 24)	4.29 (103.2)	—
	Day 10	Unchanged naldemedine	213 (30.8)	0.8 (0.5, 5.0)	1230 (14.0)	40.4 (50.5)
		Nor-naldemedine	17.6 (19.7)	3.0 (1.5, 5.0)	291.3 (19.6)	62.5 (34.7)
		Naldemedine 3-G	3.42 (28.4)	2.0 (1.5, 5.0)	32.38 (24.7)	7.2 (19.0)
		Benzamidine	1.00 (20.2)	12 (3.0, 24)	18.38 (22.5)	44.4 (268.5) [d]
30 mg	Day 1	Unchanged naldemedine	727 (26.7)	0.8 (0.5, 2.0)	3764 (13.7)	—
		Nor-naldemedine	33.9 (14.0)	4.0 (3.0, 12)	536.3 (10.7)	—
		Naldemedine 3-G	12.7 (25.3)	2.5 (1.0, 4.0)	109.2 (35.6)	—
		Benzamidine	1.16 (29.3)	24 (8.0, 24)	16.26 (39.8)	—
	Day 10	Unchanged naldemedine	700 (24.2)	0.8 (0.5, 2.5)	3744 (9.1)	45.7 (18.2)
		Nor-naldemedine	49.6 (15.9)	4.0 (2.0, 5.0)	813.1 (17.8)	73.7 (18.2)
		Naldemedine 3-G	10.7 (16.9)	2.5 (1.0, 4.0)	92.31 (29.3)	7.8 (39.0)
		Benzamidine	3.01 (27.3)	8.0 (4.0, 12)	56.42 (29.6)	17.3 (24.8)

n = 9; NC, not calculated; —, not applicable
Geometric mean (% geometric CV), a) Median (Minimum, Maximum), b) n = 0, c) n = 3, d) n = 4

6.2.3 Foreign phase I study (Mass balance study) (CTD 5.3.3.1-03, Study ID 1016V9215 [[redacted] 20[redacted] to [redacted] 20[redacted]], "Study V9215")

An open-label study was conducted at 1 site overseas to investigate the mass balance of a single oral dose of [^{14}C]-naldemedine in non-Japanese healthy adult men between 18 and 45 years of age (target sample size, 12 subjects).

A single oral dose of [^{14}C]-naldemedine 2 mg was administered under fasted conditions. Since naldemedine was shown to undergo spontaneous cleavage of the oxadiazole ring in the body, [oxadiazole-^{14}C]-naldemedine and [carbonyl-^{14}C]-naldemedine were used as [^{14}C]-naldemedine.

All 12 subjects enrolled in this study were included in the safety and pharmacokinetic analysis populations.

The incidences of adverse events were 66.7% (4 of 6 subjects) in the [oxadiazole-^{14}C]-naldemedine group and 66.7% (4 of 6 subjects) in the [carbonyl-^{14}C]-naldemedine group, and adverse events occurring in ≥2 subjects in either group are shown in Table 20. The incidences of adverse drug reactions were 50.0% (3 of 6 subjects) in the [oxadiazole-^{14}C]-naldemedine group and 50.0% (3 of 6 subjects) in the [carbonyl-^{14}C]-naldemedine group, and adverse drug reactions occurring in ≥2 subjects in either group were diarrhoea (33.3% [2 of 6 subjects] in the [oxadiazole-^{14}C]-naldemedine group, 0% [0 of 6 subjects] in the [carbonyl-^{14}C]-naldemedine group) and constipation (33.3% [2 of 6 subjects] in the [oxadiazole-^{14}C]-naldemedine group, 0% [0 of 6 subjects] in the [carbonyl-^{14}C]-naldemedine group). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

Table 20. Adverse events occurring in ≥2 subjects in either group

	[Oxadiazole-^{14}C]-naldemedine (N = 6)	[Carbonyl-^{14}C]-naldemedine (N = 6)
	Incidence %	Incidence %
Any adverse event	66.7 (4)	66.7 (4)
Diarrhoea	50.0 (3)	16.7 (1)
Nausea	0 (0)	50.0 (3)
Vomiting	0 (0)	50.0 (3)
Nasal congestion	16.7 (1)	33.3 (2)
Cough	0 (0)	33.3 (2)
Constipation	33.3 (2)	0 (0)

MedDRA/J ver.13.0; Incidence % (n)

With regard to mass balance, 57.3% and 34.8% of the administered radioactivity were recovered in urine and feces, respectively, by 288 hours post-dose in the [oxadiazole-^{14}C]-naldemedine group, and 20.4% and 64.3% of the administered radioactivity were recovered in urine and feces, respectively, by 336 hours post-dose in the [carbonyl-^{14}C]-naldemedine group.

In plasma, [^{14}C]-naldemedine predominantly existed unchanged. The $AUC_{0\text{-inf}}$ of plasma metabolites, nor-naldemedine and naldemedine 3-G, was 9.1% to 13.0% and 1.6% to 0.9% of the parent drug $AUC_{0\text{-inf}}$, respectively. Plasma concentrations of other metabolites remained below the LLOQ until the end of observation.

6.2.4 Foreign phase I study (QT/QTc study) (5.3.4.1-01, Study ID 1204V9219 [[redacted] to [redacted]], "Study V9219")

A placebo- and active-controlled, randomized, double-blind,[9)] 4-treatment, 4-period, crossover study was conducted at 1 site outside Japan to evaluate the effect of a single oral dose of naldemedine on the QT/QTc interval in non-Japanese healthy adults between 18 and 50 years of age (target sample size, 56 subjects).

A single oral dose of placebo, naldemedine 0.2 or 1 mg, or positive control moxifloxacin 400 mg was administered under fasted conditions. A ≥14-day washout period was included between the periods.

All 56 randomized subjects were included in the safety analysis population. Of the 56 subjects, 53 were included in the pharmacokinetic analysis population and 55 in the pharmacodynamic analysis population.

The incidences of adverse events were 15.2% (7 of 46 subjects) in the placebo group, 17.3% (9 of 52 subjects) in the naldemedine 0.2 mg group, 16.3% (8 of 49 subjects) in the naldemedine 1 mg group, and 10.2% (5 of 49 subjects) in the moxifloxacin group. The incidences of adverse drug reactions were 10.9% (5 of 46 subjects) in the placebo group, 5.8% (3 of 52 subjects) in the naldemedine 0.2 mg group, 10.2% (5 of 49 subjects) in the naldemedine 1 mg group, and 6.1% (3 of 49 subjects) in the moxifloxacin group. Adverse events and adverse drug reactions occurring in ≥2 subjects in any group are shown in Table 21 and Table 22. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

Table 21. Adverse events occurring in ≥2 subjects in any group

	Placebo (N = 46)	Naldemedine 0.2 mg (N = 52)	Naldemedine 1 mg (N = 49)	Moxifloxacin (N = 49)
Any adverse event	**15.2 (7)**	**17.3 (9)**	**16.3 (8)**	**10.2 (5)**
Abdominal pain	**2.2 (1)**	**3.8 (2)**	**8.2 (4)**	**0 (0)**
C-reactive protein increased	**0 (0)**	**3.8 (2)**	**4.1 (2)**	**0 (0)**
Nausea	**2.2 (1)**	**0 (0)**	**4.1 (2)**	**2.0 (1)**
Diarrhoea	**4.3 (2)**	**3.8 (2)**	**2.0 (1)**	**0 (0)**
Headache	**2.2 (1)**	**3.8 (2)**	**2.0 (1)**	**0 (0)**
Vomiting	**2.2 (1)**	**0 (0)**	**0 (0)**	**4.1 (2)**

MedDRA/J ver.16.0; Incidence % (n)

[9)] Administration of active control (moxifloxacin) was open-label.

Table 22. Adverse drug reactions occurring in ≥2 subjects in any group

	Placebo (N = 46)	Naldemedine 0.2 mg (N = 52)	Naldemedine 1 mg (N = 49)	Moxifloxacin (N = 49)
Any adverse drug reaction	**10.9 (5)**	**5.8 (3)**	**10.2 (5)**	**6.1 (3)**
Abdominal pain	**2.2 (1)**	**3.8 (2)**	**8.2 (4)**	**0 (0)**
Nausea	**2.2 (1)**	**0 (0)**	**4.1 (2)**	**2.0 (1)**
Diarrhoea	**4.3 (2)**	**3.8 (2)**	**2.0 (1)**	**0 (0)**
Vomiting	**0 (0)**	**0 (0)**	**0 (0)**	**4.1 (2)**

MedDRA/J ver.16.0; Incidence % (n)

The largest placebo-adjusted change from baseline in QTcF (ΔΔQTcF) [90% CI] was 1.3 [-0.6, 3.2] ms at 4 hours post-dose for naldemedine 0.2 mg and 0.6 [-1.4, 2.5] ms at 2 hours post-dose for naldemedine 1 mg. Since the upper bound of the 90% confidence interval was below 10 ms for both doses, the QT/QTc study was negative. The largest ΔΔQTcF was 12.6 [10.7, 14.5] ms at 4 hours post-dose in the moxifloxacin group, and the lower bound of the 90% confidence interval was above 5 ms. The study thus had assay sensitivity.

As to the plasma pharmacokinetic parameters of unchanged naldemedine, the C_{max} (geometric mean [95% CI]) was 2.4 [2.2, 2.6] ng/mL and the $AUC_{0\text{-}inf}$ was 20.1 [18.9, 21.4] ng·h/mL at the 0.2 mg dose and the C_{max} (geometric mean [95% CI]) was 11.9 [10.9, 13.0] ng/mL and the $AUC_{0\text{-}inf}$ was 103.1 [96.7, 109.9] ng·h/mL at the 1 mg dose.

6.2.5 Foreign phase I study (Effect of hepatic impairment) (CTD 5.3.3.3-02, Study ID 1402V921C [[redacted] to [redacted]], "Study V921C")

An open-label, parallel-group study was conducted at 3 sites outside Japan to assess the effect of hepatic impairment on the pharmacokinetics of a single oral dose of naldemedine in non-Japanese subjects with normal hepatic function or mild (Child-Pugh score A) or moderate (Child-Pugh score B) hepatic impairment, between 20 and 70 years of age (target sample size, 24 subjects [8 per cohort[10)]]).

A single oral dose of naldemedine 0.2 mg was administered under fasted conditions.

All 24 subjects enrolled in this study (8 per cohort) were included in the safety and pharmacokinetic analysis populations.

Adverse events occurred in 12.5% (1 of 8) of subjects with normal hepatic function, 37.5% (3 of 8) of subjects with mild hepatic impairment, and 50.0% (4 of 8) of subjects with moderate hepatic impairment; all of the events were classified as adverse drug reactions. Adverse events occurring in ≥2 subjects were diarrhoea (0% [0 of 8] of subjects with normal hepatic function, 25.0% [2 of 8] of subjects with mild hepatic impairment, 12.5% [1 of 8] of subjects with moderate hepatic impairment) and somnolence (0% [0 of 8] of subjects with normal hepatic function, 0% [0 of 8] of subjects with mild hepatic impairment, 25.0% [2 of 8] of subjects with moderate hepatic impairment). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

[10)] Subjects with normal hepatic function matched for age (± 10 years), gender, and BMI (± 20%) with subjects with moderate hepatic impairment.

As to the plasma pharmacokinetic parameters of unchanged naldemedine, the geometric mean ratios (mild or moderate hepatic impairment vs. normal hepatic function) of C_{max} and $AUC_{0\text{-}inf}$ are shown in Table 23, and there was no trend towards an increase in exposure with hepatic impairment.

Table 23. Pharmacokinetic parameters of unchanged naldemedine in healthy adults and subjects with hepatic impairment

	Naldemedine 0.2 mg	
	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng·h/mL)
Healthy adults	**2.71 (26.3)**	**23.61 (22.8)**
Subjects with mild hepatic impairment	**2.44 (47.4)**	**19.56 (35.9)**
Geometric mean ratio [90% CI][a)]	**0.90 [0.69, 1.18]**	**0.83 [0.66, 1.04]**
Subjects with moderate hepatic impairment	**2.93 (16.8)**	**24.82 (21.8)**
Geometric mean ratio [90% CI][b)]	**1.08 [0.82, 1.41]**	**1.05 [0.83, 1.33]**

n = 8, Geometric mean (% geometric CV)
a) C_{max} or $AUC_{0\text{-}inf}$ in subjects with mid hepatic impairment/C_{max} or $AUC_{0\text{-}inf}$ in healthy adults
b) C_{max} or $AUC_{0\text{-}inf}$ in subjects with moderate hepatic impairment/C_{max} or $AUC_{0\text{-}inf}$ in healthy adults

Hepatic impairment did not affect the plasma pharmacokinetic parameters of metabolites nor-naldemedine and naldemedine 3-G. Naldemedine 6-G and benzamidine were below the LLOQ in all cohorts.

6.2.6 Foreign phase I study (Effect of renal impairment) (CTD 5.3.3.3-01, Study ID 1401V921B [[redacted] 20[redacted] to [redacted] 20[redacted]], "Study V921B")

An open-label, parallel-group study was conducted at 3 sites outside Japan to assess the effect of renal impairment on the pharmacokinetics of a single oral dose of naldemedine in non-Japanese subjects with normal renal function (Clcr ≥90 mL/min), those with mild (eGFR, ≥60 and <90 mL/min/1.73m^2), moderate (eGFR, ≥30 and <60 mL/min/1.73m^2), or severe (eGFR <30 mL/min/1.73m^2, including those with end stage renal disease [ESRD] not requring hemodialysis) renal impairment, and those with ESRD requring hemodialysis, between 20 and 75 years of age (target sample size, 36-40 subjects [4-8 subjects with severe renal impairment, 8 each in other cohorts[11)]]).

A single oral dose of naldemedine 0.2 mg was administered under fasted conditions in subjects with normal renal function or mild, moderate, or severe renal impairment. In subjects with ESRD requring hemodialysis, naldemedine 0.2 mg was administered orally under fasted conditions 1 to 2 hours after the end of hemodialysis on Day 1 and 2 hours before the start of hemodialysis on Day 15.

All 41 subjects enrolled in this study (9 subjects with normal renal function, 9 subjects with mild renal impairment, 9 subjects with moderate renal impairment, 6 subjects with severe renal impairment, 8 subjects with ESRD) were included in the safety analysis population. In total, 38 subjects were included in the pharmacokinetic analysis population, excluding 2 subjects who met the exclusion criteria (history of cholecystectomy) (1 with mild renal impairment and 1 with moderate renal impairment) and 1 subject with normal renal function who met the exclusion criteria (matched for demographics with 1 subject with moderate renal impairment).

Adverse events occurred in 44.4% (4 of 9) of subjects with normal renal function, 44.4% (4 of 9) of subjects

[11)] Subjects with normal renal function matched for age (± 10 years), gender, and BMI (± 20%) with subjects with moderate renal impairment.

with mild renal impairment, 33.3% (3 of 9) of subjects with moderate renal impairment, 50.0% (3 of 6) of subjects with severe renal impairment, and 50.0% (4 of 8) of subjects with ESRD. Adverse drug reactions occurred in 22.2% (2 of 9) of subjects with normal renal function, 22.2% (2 of 9) of subjects with mild renal impairment, 33.3% (3 of 9) of subjects with moderate renal impairment, 33.3% (2 of 6) of subjects with severe renal impairment, and 50.0% (4 of 8) of subjects with ESRD. Adverse events occurring in ≥2 subjects in any cohort were nausea (0% [0 of 9] of subjects with normal renal function, 11.1% [1 of 9] of subjects with mild renal impairment, 11.1% [1 of 9] of subjects with moderate renal impairment, 0% [0 of 6] of subjects with severe renal impairment, 25.0% [2 of 8] of subjects with ESRD) and headache (33.3% [3 of 9] of subjects with normal renal function, 11.1% [1 of 9] of subjects with mild renal impairment, 0% [0 of 6] of subjects with moderate renal impairment, 0% [0 of 6] of subjects with severe renal impairment, 12.5% [1 of 8] of subjects with ESRD), and except for headache occurring in 1 subject with normal renal function, all these events were classified as adverse drug reactions. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

The geometric mean ratios (varying degrees of renal impairment vs. normal renal function) of C_{max} and $AUC_{0\text{-}inf}$ of unchanged naldemedine are shown in Table 24.

Table 24. Pharmacokinetic parameters of unchanged naldemedine in heathy adults and subjects with renal impairment

	Naldemedine 0.2 mg	
	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng·h/mL)
Healthy adults	**3.39 (20.7)**	**23.55 (18.9)**
Subjects with mild renal impairment	**3.01 (23.7)**	**25.35 (24.6)**
Geometric mean ratio [90% CI][a)]	**0.89 [0.74, 1.07]**	**1.08 [0.90, 1.28]**
Subjects with moderate renal impairment	**2.56 (25.5)**	**24.97 (23.6)**
Geometric mean ratio [90% CI][b)]	**0.75 [0.63, 0.91]**	**1.06 [0.89, 1.26]**
Subjects with severe renal impairment [c)]	**2.76 (13.4)**	**32.44 (18.1)**
Geometric mean ratio [90% CI][d)]	**0.81 [0.66, 1.00]**	**1.38 [1.14, 1.67]**
Dosing after hemodialysis [e)] in ESRD subjects	**2.81 (24.8)**	**19.49 (17.9)**
Dosing before hemodialysis [f)] in ESRD subjects	**2.23 (26.5)**	**18.63 (26.1)**
Geometric mean ratio [90% CI][g)]	**0.83 [0.69, 1.00]**	**0.83 [0.69, 0.99]**

n = 8, Geometric mean (% geometric CV)
a) C_{max} or $AUC_{0\text{-}inf}$ in subjects with mild renal impairment/C_{max} or $AUC_{0\text{-}inf}$ in healthy adults
b) C_{max} or $AUC_{0\text{-}inf}$ in subjects with moderate renal impairment/C_{max} or $AUC_{0\text{-}inf}$ in healthy adults
c) n = 6
d) C_{max} or $AUC_{0\text{-}inf}$ in subjects with severe renal impairment/C_{max} or $AUC_{0\text{-}inf}$ in healthy adults
e) Dosing 1 to 2 hours after the end of hemodialysis
f) Dosing 2 hours before the start of hemodialysis
g) C_{max} or $AUC_{0\text{-}inf}$ after dosing 1 to 2 hours after the end of hemodialysis in subjects with ESRD/C_{max} or $AUC_{0\text{-}inf}$ in healthy adults

With regard to the plasma pharmacokinetic parameters of the metabolites of naldemedine, renal impairment did not affect the C_{max} of nor-naldemedine. Meanwhile, the $AUC_{0\text{-}last}$ of nor-naldemedine was approximately 1.68 times higher in subjects with severe renal impairment and approximately 2.80 times higher in subjects with ESRD, than in subjects with normal renal function. Benzamidine was below the LLOQ in all cohorts.

6.2.7 Foreign phase I studies (Drug interaction studies with P-gp inhibitor, CYP3A inducer, and CYP3A inhibitors) (CTD 5.3.3.4-01 to 5.3.3.4-03; Study ID 1202V9218 [[redacted] to [redacted]], "Study V9218"; Study ID 1403V921D [[redacted] to [redacted]], "Study V921D"; Study ID 1502V921E [[redacted] to [redacted]], "Study V921E")

Three foreign phase I studies (Studies V9218, V921D, and V921E) were conducted to evaluate the effects of cyclosporine (a P-gp inhibitor), rifampicin (a CYP3A inducer), and itraconazole and fluconazole (CYP3A inhibitors) on the pharmacokinetics of naldemedine in non-Japanese healthy adults.

The pharmacokinetic parameters of naldemedine are shown in Table 25.

Table 25. Plasma pharmacokinetic parameters of naldemedine administered with or without test drugs

Study ID	Naldemedine dose	Coadministered drug (oral)	N		C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng·h/mL)
V9218 [a]	0.4 mg	Cyclosporine 600 mg	13	Without coadministered drug	4.86 (14.5)	38.94 (17.3)
				With coadministered drug	7.03 (25.0)	69.55 (19.2)
				Geometric mean ratio [90% CI][b]	1.45 [1.27, 1.66]	1.78 [1.57, 2.02]
V921D [c]	0.2 mg	Rifampicin 600 mg	14	Without coadministered drug	2.72 (25.7)	21.77 (19.2)
				With coadministered drug	1.68 (21.1)	3.70 (16.0)
				Geometric mean ratio [90% CI][d]	0.62 [0.55, 0.70]	0.17 [0.15, 0.19]
V921E	0.2 mg	Itraconazole 200 mg [e]	14	Without coadministered drug	3.56 (38.2)	26.98 (37.7)
				With coadministered drug	4.00 (20.2)	78.64 (35.3)
				Geometric mean ratio [90% CI][f]	1.12 [0.97, 1.30]	2.91 [2.64, 3.22]
	0.2 mg	Fluconazole 200 mg [g]	14	Without coadministered drug	3.48 (23.7)	27.18 (16.5)
				With coadministered drug	4.81 (16.1)	51.60 (13.5)
				Geometric mean ratio [90% CI][h]	1.38 [1.23, 1.55]	1.90 [1.80, 2.00]

Geometric mean (% geometric CV)

a) A single oral dose of naldemedine 0.4 mg was administered in Period I or II, and naldemedine 0.4 mg was coadministered with cyclosporine 600 mg in Period II or I.

b) C_{max} or $AUC_{0\text{-}inf}$ with cyclosporine/C_{max} or $AUC_{0\text{-}inf}$ without cyclosporine

c) A single dose of naldemedine 0.2 mg was administered on Day 1, and rifampicin 600 mg was administered once daily on Days 4 to 20, with naldemedine 0.2 mg coadministered on Day 18.

d) C_{max} or $AUC_{0\text{-}inf}$ with rifampicin/C_{max} or $AUC_{0\text{-}inf}$ without rifampicin

e) A single dose of naldemedine 0.2 mg was administered on Day 1, itraconazole 200 mg was administered twice daily on Day 5, and itraconazole 200 mg was administered once daily on Days 6 to 11, with naldemedine 0.2 mg coadministered on Day 9.

f) C_{max} or $AUC_{0\text{-}inf}$ with itraconazole/C_{max} or $AUC_{0\text{-}inf}$ without itraconazole

g) A single dose of naldemedine 0.2 mg was administered on Day 1, fluconazole 400 mg was administered once daily on Day 5, and fluconazole 200 mg was administered once daily on Days 6 to 11, with naldemedine 0.2 mg coadministered on Day 9.

h) C_{max} or $AUC_{0\text{-}inf}$ with fluconazole/C_{max} or $AUC_{0\text{-}inf}$ without fluconazole

6.2.8 Multi-regional (Japan and Korea) phase II study in patients with cancer (CTD 5.3.5.1-01, Study ID 1108V9222 [[redacted] to [redacted]], "Study V9222")

For a brief description of the study, see Section 7.1.

The pharmacokinetics of naldemedine were evaluated in Japanese and Korean patients with cancer and OIC who were aged ≥18 years (Table 36) (target sample size, 212 subjects [53 per group]) following the first dose of naldemedine.

Of 227 randomized subjects (57 in the placebo group, 56 in the naldemedine 0.1 mg group, 58 in the naldemedine 0.2 mg group, 56 in the naldemedine 0.4 mg group), 38 (10 in the 0.1 mg group, 16 in the 0.2 mg group, 12 in the 0.4 mg group [all Japanese subjects]) were included in the pharmacokinetic analysis population.

The pharmacokinetic parameters are shown in Table 26.

Table 26. Plasma pharmacokinetic parameters of unchanged naldemedine in Japanese patients with cancer and OIC

Naldemedine dose	n	C_{max} (ng/mL)	t_{max} [a)] (h)	$AUC_{0\text{-inf}}$ (ng·h/mL)	$t_{1/2}$ (h)
0.1 mg	**10**	**1.32 (34.0)**	**1.93 (1.00, 7.92)**	**12.29 (28.8)[b)]**	**8.96 (37.0)[c)]**
0.2 mg	**16**	**2.02 (31.4)**	**2.00 (0.96, 11.50)**	**23.79 (19.7)[c)]**	**9.53 (19.7)[d)]**
0.4 mg	**12**	**4.80 (36.9)**	**1.92 (0.92, 7.64)**	**42.20 (26.4)[b)]**	**10.1 (19.9)[e)]**

Geometric mean (% geometric CV)
a) Median (Minimum, Maximum), b) n = 4, c) n = 8, d) n = 13, e) n = 10

6.2.9 Foreign phase II study in patients with chronic non-cancer pain (CTD 5.3.5.1-04 [Reference data], Study ID 1107V9221 [August 2011 to August 2012], "Study V9221")

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 55 sites outside Japan to evaluate the safety and pharmacokinetics, etc. of naldemedine in non-Japanese patients aged ≥18 years who had OIC and chronic non-cancer pain[12)] (target sample size, 240 subjects [60 per group]).

Placebo or naldemedine 0.1, 0.2, or 0.4 mg was administered orally once daily for 28 days.

Among 244 randomized subjects (61 per group), 243 (61 in the placebo group, 61 in the naldemedine 0.1 mg group, 60 in the naldemedine 0.2 mg group, 61 in the naldemedine 0.4 mg group) were included in the safety analysis population (excluding 1 subject who did not receive study drug [in the 0.2 mg group]). In total, 28 naldemedine-treated subjects (9 in the 0.1 mg group, 9 in the 0.2 mg group, and 10 in the 0.4 mg group) were included in the pharmacokinetic analysis population.

The pharmacokinetic parameters are shown in Table 27.

Table 27. Plasma pharmacokinetic parameters of unchanged naldemedine in non-Japanese patients with OIC and chronic non-cancer pain

	Naldemedine dose	n	C_{max} (ng/mL)	t_{max} (h)[a)]	$AUC_{0\text{-}\tau}$ (ng·h/mL)	$t_{1/2}$ (h)
Day 1	**0.1 mg**	**9**	**0.99 (41.1)**	**1.00 (0.97, 2.27)**	**8.49 (24.5)[b)]**	**8.38 (19.9)[b)]**
	0.2 mg	**9**	**1.89 (48.2)**	**1.03 (0.97, 4.02)**	**15.95 (42.6)[c)]**	**8.47 (35.9)[d)]**
	0.4 mg	**10**	**3.67 (41.3)**	**1.03 (0.95, 4.00)**	**30.58 (26.9)[d)]**	**8.04 (14.4)[e)]**
Day 28	**0.1 mg**	**4**	**1.15 (25.8)**	**1.03 (1.00, 1.97)**	**9.68 (33.7)[f)]**	**8.64 (16.4)[f)]**
	0.2 mg	**4**	**2.00 (22.7)**	**1.00 (1.00, 1.03)**	**16.94 (46.6)**	**7.11 (28.7)**
	0.4 mg	**4**	**4.03 (32.3)**	**1.00 (1.00, 1.08)**	**31.72 (11.4)[f)]**	**10.8 (31.5)[f)]**

Geometric mean (% geometric CV)
a) Median (Minimum, Maximum), b) n = 6, c) n = 8, d) n = 7, e) n = 5, f) n = 3

[12)] Patients who met the following inclusion criteria:
- Opioid therapy for ≥3 months, including a ≥1 month treatment with a stable opioid dose of ≥30 mg/day oral morphine equivalents.
- In the 2 weeks prior to the initiation of study treatment, <3 SBMs per week with ≥25% of BMs accompanied by ≥1 of the following conditions: straining, feeling of incomplete evacuation, lumpy or hard stools.

The incidences of adverse events were 50.8% (31 of 61 subjects) in the placebo group, 41.0% (25 of 61 subjects) in the naldemedine 0.1 mg group, 50.0% (30 of 60 subjects) in the naldemedine 0.2 mg group, and 55.7% (34 of 61 subjects) in the naldemedine 0.4 mg group. The incidences of adverse drug reactions were 16.4% (11 of 61 subjects) in the placebo group, 16.4% (10 of 61 subjects) in the naldemedine 0.1 mg group, 25.0% (15 of 60 subjects) in the naldemedine 0.2 mg group, and 39.3% (24 of 61 subjects) in the naldemedine 0.4 mg group. Adverse events and adverse drug reactions occurring in ≥5.0% of subjects in any group are shown in Table 28 and Table 29, respectively.

Table 28. Adverse events occurring in ≥5.0% of subjects in any group

	Placebo (N = 61)	Naldemedine 0.1 mg (N = 61)	Naldemedine 0.2 mg (N = 60)	Naldemedine 0.4 mg (N = 61)
Any adverse event	50.8 (31)	41.0 (25)	50.0 (30)	55.7 (34)
Diarrhoea	4.9 (3)	4.9 (3)	5.0 (3)	18.0 (11)
Abdominal pain	1.6 (1)	4.9 (3)	8.3 (5)	14.8 (9)
Urinary tract infection	1.6 (1)	1.6 (1)	5.0 (3)	6.6 (4)
Abdominal pain upper	0 (0)	1.6 (1)	3.3 (2)	6.6 (4)
Nausea	1.6 (1)	1.6 (1)	6.7 (4)	4.9 (3)
Flatulence	3.3 (2)	4.9 (3)	5.0 (3)	3.3 (2)
Arthralgia	6.6 (4)	1.6 (1)	1.7 (1)	1.6 (1)
Back pain	6.6 (4)	1.6 (1)	0 (0)	1.6 (1)

MedDRA ver.13.1; Incidence % (n)

Table 29. Adverse drug reactions occurring in ≥5.0% of subjects in any group

	Placebo (N = 61)	Naldemedine 0.1 mg (N = 61)	Naldemedine 0.2 mg (N = 60)	Naldemedine 0.4 mg (N = 61)
Any adverse drug reaction	16.4 (10)	16.4 (10)	25.0 (15)	39.3 (24)
Abdominal pain	1.6 (1)	3.3 (2)	8.3 (5)	14.8 (9)
Diarrhoea	3.3 (2)	1.6 (1)	3.3 (2)	14.8 (9)
Nausea	0 (0)	1.6 (1)	6.7 (4)	4.9 (3)
Flatulence	3.3 (2)	4.9 (3)	5.0 (3)	3.3 (2)

MedDRA ver.13.1; Incidence % (n)

No deaths were reported. Serious adverse events occurred in 3.3% (2 of 61) of subjects in the naldemedine 0.1 mg group (chest pain and appendicitis in 1 subject each) and 1.6% (1 of 61) of subjects in the naldemedine 0.4 mg group (left ventricular dysfunction), but a causal relationship to study drug was ruled out for all these events. Of these events, chest pain in 1 subject in the naldemedine 0.1 mg group led to treatment discontinuation.

6.2.10 Study that evaluated pharmacokinetics in subjects receiving morphine sulfate (CTD 5.3.5.4-01 [Reference data], Study ID V9216 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 2 sites outside Japan to evaluate the effect of naldemedine on the pharmacokinetics of morphine sulfate and the safety etc. of coadministration of naldemedine and morphine sulfate in non-Japanese healthy adult men and women between 18 and 55 years of age (target sample size, 80 subjects [20 per group]).

A single oral dose of placebo or naldemedine 0.1, 1, or 10 mg was administered. One hour later, 0.1 to 0.3 mg/kg of morphine sulfate was intravenously infused over ≥20 minutes.

All 80 randomized subjects (20 per group) were included in the safety analysis population and all of 60 subjects who received naldemedine were included in the pharmacokinetic analysis population.

The pharmacokinetic parameters are shown in Table 30.

Table 30. Plasma pharmacokinetic parameters following coadministration of naldemedine and morphine sulfate

	Naldemedine dose	n	C_{max} (ng/mL)	t_{max} (h)[a)]	AUC_{0-t} (ng·h/mL)
Unchanged naldemedine	0.1 mg	20	1.15 (23.9)	0.97 (0.50, 1.52)	5.18 (18.5)
	1 mg	20	10.2 (22.7)	0.97 (0.50, 1.68)	50.6 (11.3)
	10 mg	20	102 (35.8)	1.50 (0.53, 6.00)	503 (34.0)
Nor-naldemedine	0.1 mg	2	0.16 (NC)	8.73 (8.47, 9.00)	0.23 (NC)
	1 mg	20	0.67 (34.3)	6.00 (4.00, 9.00)	4.48 (32.3)
	10 mg	20	7.16 (40.3)	6.00 (3.00, 9.03)	47.3 (43.7)
Unchanged morphine	0.1 mg	11	235 (61.7)	0.30 (0.30, 0.38)	239 (52.7)
	1 mg	10	192 (47.6)	0.30 (0.30, 0.50)	208 (53.7)
	10 mg	10	219 (43.3)	0.30 (0.30, 0.50)	204 (44.5)
Morphine-6-glucuronide	0.1 mg	20	46 (62.6)	0.50 (0.50, 4.00)	216 (47.2)[b)]
	1 mg	20	38 (49.9)	0.50 (0.50, 4.10)	187 (40.8)[b)]
	10 mg	20	48 (26.8)	0.50 (0.50, 4.00)	215 (27.9)
Morphine-3-glucuronide	0.1 mg	20	315 (58.5)	0.50 (0.50, 0.57)	1414 (45.2)[b)]
	1 mg	20	270 (44.8)	0.50 (0.30, 0.50)	1234 (35.7)[b)]
	10 mg	20	332 (25.7)	0.50 (0.50, 0.57)	1396 (27.9)

Geometric mean (% geometric CV)
a) Median (Minimum, Maximum), b) n = 19

Adverse events occurred in all subjects in all groups. Common adverse events were vomiting, hyperhidrosis, pruritus, feeling hot, and flushing; these events were considered to be induced by morphine sulfate. The incidences of adverse drug reactions were 10.0% (2 of 20 subjects) in the placebo group, 30.0% (6 of 20 subjects) in the naldemedine 0.1 mg group, 40.0% (8 of 20 subjects) in the naldemedine 1 mg group, and 50.0% (10 of 20 subjects) in the naldemedine 10 mg group. Adverse drug reactions occurring in ≥2 subjects in any group are shown in Table 31.

Table 31. Adverse drug reactions occurring in ≥2 subjects in any group

	Placebo (N = 20)	Naldemedine 0.1 mg (N = 20)	Naldemedine 1 mg (N = 20)	Naldemedine 10 mg (N = 20)
Any adverse drug reaction	10.0 (2)	30.0 (6)	40.0 (8)	50.0 (10)
Headache	5.0 (1)	25.0 (5)	30.0 (6)	25.0 (5)
Diarrhoea	0 (0)	0 (0)	0 (0)	15.0 (3)
Abdominal pain upper	0 (0)	0 (0)	0 (0)	10.0 (2)
Urinary hesitation	5.0 (1)	0 (0)	10.0 (2)	0 (0)

MedDRA ver.14.0; Incidence % (n)

There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

Based on the above results, the AUC_{0-t} and C_{max} values of morphine and its metabolites were similar across all naldemedine dose groups. The applicant explained that naldemedine does not affect the pharmacokinetics of morphine over the dose range of 0.1 to 10 mg.

6.R Outline of the review conducted by PMDA

6.R.1 Food effect

The applicant's explanation on the effect of food on the pharmacokinetics of naldemedine:

Study V921A in non-Japanese healthy adults [see Section 6.1.1] evaluated the effect of food on the pharmacokinetics of naldemedine. The C_{max} was reduced by approximately 35% under fed conditions compared with fasted conditions, and the t_{max} was prolonged from 0.75 hours under fasted conditions to 2.50 hours under fed conditions, suggesting delayed absorption due to food. On the other hand, food had no effect on the $AUC_{0\text{-}inf}$. In a multi-regional (Japan and Korea) phase II study (Study V9222) and Japanese phase III studies (Studies V9236, V9237, V9238, and V9239), naldemedine was administered without regard to meals, and there were no particular problems with the efficacy or safety of naldemedine. Thus, the changes in the C_{max} and t_{max} with food observed in Study V921A in non-Japanese healthy adults are not considered clinically relevant. Hence, naldemedine can be administered without regard to meals.

PMDA accepted the applicant's explanation.

6.R.2 Use of naldemedine in patients with renal impairment

The applicant's explanation on the pharmacokinetics of naldemedine in patients with renal impairment:

In Study V921B, the $AUC_{0\text{-}inf}$ of naldemedine was approximately 1.38 times higher in subjects with severe renal impairment than in subjects with normal renal function. However, the incidence of adverse events in subjects with renal impairment did not tend to increase compared with that in subjects with normal renal function; severe renal impairment is thus unlikely to increase the safety risk of naldemedine. In a multi-regional (Japan and Korea) phase II study in patients with cancer (Study V9222), naldemedine exposure at 0.4 mg dose was approximately 2-fold higher than that at 0.2 mg dose, but there were no major differences in the occurrence of adverse events between the 0.4 and 0.2 mg groups. Thus, an approximately 2-fold increase in exposure is unlikely to cause safety problems. Based on the above, at present, the package insert need not include a precautionary statement concerning use of naldemedine in patients with severe renal impairment.

PMDA accepted the applicant's explanation.

6.R.3 Drug interactions

The applicant's explanation on naldemedine drug interactions:

Precautions about interactions with CYP3A4 inhibitors (itraconazole, etc.) and inducer (rifampicin) will be provided in the package insert since these drug interactions were observed in foreign drug interaction studies (Studies V9218, V921D, and V921E) [see Section 6.2.7].

A foreign drug interaction study (Study V9218) assessed pharmacokinetic interactions between naldemedine and a P-gp inhibitor, cyclosporine. As a result, coadministration with cyclosporine increased the C_{max} and $AUC_{0\text{-}inf}$ of unchanged naldemedine by 1.45-fold and 1.78-fold, respectively, compared with oral administration of naldemedine alone, whereas there were no major differences in the incidence of adverse events between naldemedine with and without the P-gp inhibitor [see Section 6.2.7].

In Japanese and foreign clinical studies, the effect of concomitant P-gp inhibitor (as patient characteristics) on safety was evaluated. The results are shown in Table 32.

Table 32. Incidence of adverse events with or without concomitant P-gp inhibitor

		With concomitant P-gp inhibitor	Without concomitant P-gp inhibitor
Japanese studies	Pooled controlled studies in patients with cancer (V9222, V9236)	54.5% (6/11) (Pooled placebo group, 33.3% [1/3])	67.4% (97/144) (Pooled placebo group, 50.3% [75/149])
	Extension study in patients with cancer (V9237)	71.4% (5/7)	80.6% (100/124)
	Pooled uncontrolled studies in patients with chronic non-cancer pain (V9238, V9239)	100% (7/7)	87.0% (40/46)
Foreign studies	Pooled controlled studies in patients with chronic non-cancer pain (V9231, V9232, V9235) [a)]	66.7% (72/108) (Pooled placebo group, 61.0% [64/105])	43.9% (451/1027) (Pooled placebo group, 43.1% [446/1036])

a) Data up to Week 12

The number of patients who received concomitant P-gp inhibitor was limited in Japanese studies and rigorous comparison could not be made, but the incidence of adverse events tended to be similar to that in the placebo group. Hence, there should be no major differences in the incidence of adverse events between patients treated with naldemedine with and without a P-gp inhibitor. Also in foreign studies, the incidence of adverse events was slightly higher in patients who received concomitant P-gp inhibitor, but there was no problematic trend compared to the incidence of adverse events in patients treated with placebo with or without concomitant P-gp inhibitor. Based on the above, at present, the package insert need not include a precautionary statement about interactions between naldemedine and P-gp inhibitors.

PMDA's view:

So far, no particular safety concerns have been raised about concomitant use of naldemedine with P-gp inhibitors in clinical studies. However, since coadministration of a P-gp inhibitor increased the C_{max} and AUC_{0-inf} in a foreign drug-interaction study (Study V9218), etc., a relevant precaution should be provided in the package insert. PMDA will draw a final conclusion on the need for a precautionary statement in the package insert, taking account of comments from the Expert Discussion.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted evaluation data, in the form of the results from 1 multi-regional (Japan and Korea) phase II study and 4 Japanese phase III studies in patients with opioid-induced constipation (Table 33). The definitions of main endpoints in phase II and III studies are shown in Table 34 and Bristol Stool Form Scale (BSS) in Table 35.

Table 33. Summary of efficacy and safety evaluation data

Phase	Study ID	Population	Design	Duration	Group (No. of subjects)	Efficacy endpoint
Phase II	V9222	Patients with cancer	Double-blind, parallel-group	14 days	Placebo (N = 56) Naldemedine 0.1 mg (N = 56) Naldemedine 0.2 mg (N = 58) Naldemedine 0.4 mg (N = 56)	Change from baseline in weekly frequency of SBMs over 2-week treatment period (Least-squares mean ± SE) Placebo: 1.50 ± 0.68 Naldemedine 0.1 mg: 3.43 ± 0.69 Naldemedine 0.2 mg: 4.75 ± 0.67 Naldemedine 0.4 mg: 7.29 ± 0.68
Phase III	V9236	Patients with cancer	Double-blind, parallel-group	14 days	Placebo (N = 96) Naldemedine 0.2 mg (N = 97)	SBM responder rate during 2-week treatment period Placebo: 34.4% Naldemedine 0.2 mg: 71.1%
Phase III	V9237	Patients with cancer	Open-label, uncontrolled	12 weeks	Naldemedine 0.2 mg (N = 131)	Change in PAC-SYM score at last observation (Mean ± SD) Naldemedine 0.2 mg: −0.42 ± 0.54 Change in PAC-QOL score at last observation (Mean ± SD) Naldemedine 0.2 mg: −0.40 ± 0.56
Phase III	V9238	Patients with chronic non-cancer pain	Open-label, uncontrolled	48 weeks	Naldemedine 0.2 mg (N = 43)	SBM responder rate during the first 2 weeks of the treatment period Naldemedine 0.2 mg: 81.0%
Phase III	V9239	Patients with chronic non-cancer pain	Open-label, uncontrolled	48 weeks	Naldemedine 0.2 mg (N = 10)	SBM responder rate during the first 2 weeks of the treatment period Naldemedine 0.2 mg: 90.0%

Table 34. Main efficacy endpoints and assessment method

SBM	A BM without rescue laxative taken within the past 24 hours
Weekly frequency of SBMs	7× (Total number of SBMs during the observation period)/(Number of days of observation)
SBM responder rate	Proportion of patients with ≥3 SBMs per week and an increase of ≥1 SBM per week from baseline
Change from baseline in frequency of SBMs	(Number of SBMs per week during 2-week treatment period) － (Number of SBMs per week during 14 days prior to formal enrollment)
CSBM	An SBM accompanied by the feeling of complete evacuation
CSBM responder rate	Proportion of patients with ≥3 CSBMs per week and an increase of ≥1 CSBM per week from baseline
PAC-SYM	Each of 12 symptoms of constipation in 3 domains (abdominal, rectal, and stool symptoms) in the past 2 weeks was scored by patients on the following 5-point scale. 0, absence of symptoms; 1, mild; 2, moderate; 3, severe; 4, very severe
PAC-QOL	For assessment of constipation QOL in the past 2 weeks, each of 28 items in 4 domains (physical discomfort, psychological discomfort, worries and concerns, dissatisfaction) was scored by patients using the following 5-point scale. 0, not at all/none of the time; 1, a little bit/a little of the time; 2, moderately/some of the time; 3, quite a bit/most of the time; 4, extremely/all of the time

Table 35. Bristol Stool Form Scale (BSS)

1	Separate hard lumps like nuts (difficult to pass)
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 (pass easily)
6	Fluffy pieces with ragged edges/mushy stool
7	Watery, no solid pieces, entirely liquid

7.1 Phase II study

7.1.1 Multi-regional (Japan and Korea) phase II study in patients with cancer (CTD 5.3.5.1-01, Study ID 1108V9222 [[redacted] to [redacted]], "Study V9222")

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 102 sites (91 in Japan, 11 in Korea) to evaluate the efficacy and safety of naldemedine in Japanese and Korean patients with cancer and OIC who were aged ≥18 years (Table 36) (target sample size, 212 subjects [53 per group]). The applicant considered that conducting the study only in Japan was unfeasible because of the limited number of Japanese patients that could be enrolled. The study therefore enrolled Korean patients as well, because there were no major differences in medical practice (e.g., the use of opioid analgesics for the treatment of cancer pain and treatments for OIC such as laxatives) between Japan and Korea.

Table 36. Key inclusion criteria for patients with cancer and OIC

● Regular opioid use for ≥2 weeks, and a stable opioid regimen for 14 days prior to formal enrollment
● ≤5 SBMs with ≥1 of the following symptoms in ≥25% of BMs during 14 days prior to formal enrollment:
・Straining (Straining score[13] ≥2 [moderate])
・Feeling of incomplete evacuation
・Hard or lumpy stools (BSS [Table 35] 1 or 2)

Placebo or naldemedine 0.1, 0.2, or 0.4 mg was administered orally once daily for 14 days. Patients receiving regular laxative agents at the time of enrollment were required to maintain the laxative regimen. Dose reduction of regular opioids, changes in dosage regimen, or changes of drug or dosage form were not allowed. (However, dose increase was permitted if considered necessary by the investigator due to increased pain, and use of rescue opioid was allowed in the event of sudden pain.)

Of 227 randomized subjects (57 in the placebo group, 56 in the naldemedine 0.1 mg group, 58 in the naldemedine 0.2 mg group, 56 in the naldemedine 0.4 mg group), 226 subjects (56 in the placebo group [54 Japanese subjects], 56 in the 0.1 mg group [53 Japanese subjects], 58 in the 0.2 mg group [54 Japanese subjects], 56 in the 0.4 mg group [53 Japanese subjects]) were included in the safety analysis population. (The remaining 1 subject [in the placebo group] was excluded.) Of the 226 subjects in the safety analysis population, 225 (56 in the placebo group [54 Japanese subjects], 55 in the 0.1 mg group [52 Japanese subjects], 58 in the 0.2 mg group [54 Japanese subjects], 56 in the 0.4 mg group [53 Japanese subjects]) were included in the FAS, which was used as the primary efficacy analysis population. (The remaining 1 subject was excluded because of lack of efficacy endpoint data [the 0.1 mg group].) There were 20 withdrawals (4 in the placebo group, 4 in the 0.1 mg group, 4 in the 0.2 mg group, 8 in the 0.4 mg group). The reasons for withdrawals were adverse events (9 subjects [1 in the placebo group, 3 in the 0.1 mg group, 1 in the 0.2 mg group, 4 in the 0.4 mg group]), patient's request (6 subjects [1 in the placebo group, 1 in the 0.1 mg group, 1 in the 0.2 mg group, 3 in the 0.4 mg group]), others (4 subjects [1 in the placebo group, 2 in the 0.2 mg group, 1 in the 0.4 mg group]), and ineligibility (1 in the placebo group).

[13] Severity of straining with the BM was scored on a 5-point scale (0, no straining; 1, mild straining; 2, moderate straining; 3, severe straining; 4, very severe straining).

The primary efficacy endpoint was the change from baseline in weekly frequency of SBMs over the 2-week treatment period (for results, see Table 37). Statistically significant differences were observed between each dose of naldemedine and placebo ($P < 0.0001$ for 0.4 mg, $P = 0.0007$ for 0.2 mg, 0.0465 for 0.1 mg; analysis of covariance [ANCOVA], two-sided significance level of 5%, closed testing procedure for multiplicity adjustment).

Table 37. Change from baseline in weekly frequency of SBMs over 2-week treatment period (FAS)

	Placebo (N = 56)	Naldemedine 0.1 mg (N = 55)	Naldemedine 0.2 mg (N = 58)	Naldemedine 0.4 mg (N = 56)
Baseline weekly frequency of SBMs (Mean ± SD)	0.99 ± 0.79	0.95 ± 0.82	1.04 ± 0.92	1.06 ± 0.91
Weekly frequency of SBMs during treatment period (Mean ± SD)	2.49 ± 2.95	4.39 ± 3.56	5.79 ± 3.74	8.35 ± 8.35
Change in frequency of SBMs (Least-squares mean ± SE)	1.50 ± 0.68	3.43 ± 0.69	4.75 ± 0.67	7.29 ± 0.68
Treatment difference in change in frequency of SBMs (Naldemedine − Placebo) [95% CI]	—	1.93 [0.03, 3.83]	3.25 [1.38, 5.13]	5.79 [3.90, 7.68]
P-value[a)]	—	0.0465	0.0007	< 0.0001

a) ANCOVA model with treatment group as a fixed effect and baseline weekly frequency of SBMs as a covariate. Two-sided significance level of 5%. A sequential step-down, closed testing procedure to account for multiplicity.

The incidences of adverse events were 75.0% (42 of 56 subjects) in the placebo group, 82.1% (46 of 56 subjects) in the 0.1 mg group, 84.5% (49 of 58 subjects) in the 0.2 mg group, and 83.9% (47 of 56 subjects) in the 0.4 mg group. The incidences of adverse drug reactions were 39.3% (22 of 56 subjects) in the placebo group, 41.1% (23 of 56 subjects) in the 0.1 mg group, 46.6% (27 of 58 subjects) in the 0.2 mg group, and 57.1% (32 of 56 subjects) in the 0.4 mg group. Adverse events and adverse drug reactions occurring in ≥5.0% of subjects in any group are shown in Table 38 and Table 39, respectively.

Table 38. Adverse events occurring ≥5.0% of subjects in any group

	Placebo (N = 56)	Naldemedine 0.1 mg (N = 56)	Naldemedine 0.2 mg (N = 58)	Naldemedine 0.4 mg (N = 56)
Any adverse event	**75.0 (42)**	**82.1 (46)**	**84.5 (49)**	**83.9 (47)**
Diarrhoea	**30.4 (17)**	**28.6 (16)**	**44.8 (26)**	**57.1 (32)**
Decreased appetite	**3.6 (2)**	**5.4 (3)**	**10.3 (6)**	**10.7 (6)**
White blood cell count decreased	**14.3 (8)**	**3.6 (2)**	**10.3 (6)**	**8.9 (5)**
Nausea	**8.9 (5)**	**8.9 (5)**	**6.9 (4)**	**5.4 (3)**
Abdominal pain	**0 (0)**	**3.6 (2)**	**5.2 (3)**	**5.4 (3)**
Vomiting	**0 (0)**	**8.9 (5)**	**3.4 (2)**	**5.4 (3)**
Bone marrow failure	**3.6 (2)**	**0 (0)**	**3.4 (2)**	**5.4 (3)**
Protein total decreased	**3.6 (2)**	**5.4 (3)**	**10.3 (6)**	**3.6 (2)**
Nasopharyngitis	**3.6 (2)**	**0 (0)**	**5.2 (3)**	**3.6 (2)**
Anaemia	**5.4 (3)**	**3.6 (2)**	**1.7 (1)**	**3.6 (2)**
Dizziness	**5.4 (3)**	**0 (0)**	**0 (0)**	**3.6 (2)**
Blood pressure increased	**0 (0)**	**5.4 (3)**	**0 (0)**	**1.8 (1)**
Blood urea increased	**1.8 (1)**	**3.6 (2)**	**8.6 (5)**	**0 (0)**
Protein urine present	**1.8 (1)**	**14.3 (8)**	**6.9 (4)**	**0 (0)**
Blood ALP increased	**7.1 (4)**	**0 (0)**	**6.9 (4)**	**0 (0)**
ALT increased	**1.8 (1)**	**0 (0)**	**6.9 (4)**	**0 (0)**
AST increased	**1.8 (1)**	**0 (0)**	**6.9 (4)**	**0 (0)**
Somnolence	**3.6 (2)**	**1.8 (1)**	**5.2 (3)**	**0 (0)**
Malaise	**1.8 (1)**	**1.8 (1)**	**5.2 (3)**	**0 (0)**
Hypertension	**0 (0)**	**1.8 (1)**	**5.2 (3)**	**0 (0)**
GGT increased	**7.1 (4)**	**0 (0)**	**5.2 (3)**	**0 (0)**
Abdominal pain upper	**1.8 (1)**	**0 (0)**	**5.2 (3)**	**0 (0)**
Red blood cell count decreased	**0 (0)**	**5.4 (3)**	**3.4 (2)**	**0 (0)**
Haemoglobin decreased	**5.4 (3)**	**1.8 (1)**	**3.4 (2)**	**0 (0)**
Haematocrit decreased	**5.4 (3)**	**1.8 (1)**	**1.7 (1)**	**0 (0)**

MedDRA/J ver.15.1; Incidence % (n)

Table 39. Adverse drug reactions occurring in ≥5.0% of subjects in any group

	Placebo (N = 56)	Naldemedine 0.1 mg (N = 56)	Naldemedine 0.2 mg (N = 58)	Naldemedine 0.4 mg (N = 56)
Any adverse drug reaction	**39.3 (22)**	**41.1 (23)**	**46.6 (27)**	**57.1 (32)**
Diarrhoea	**23.2 (13)**	**25.0 (14)**	**36.2 (21)**	**50.0 (28)**
Abdominal pain	**0 (0)**	**3.6 (2)**	**1.7 (1)**	**5.4 (3)**
Abdominal pain upper	**0 (0)**	**0 (0)**	**5.2 (3)**	**0 (0)**
Protein urine present	**1.8 (1)**	**5.4 (3)**	**1.7 (1)**	**0 (0)**

MedDRA/J ver.15.1; Incidence % (n)

Deaths occurred in 5.4% (3 of 56) of subjects in the placebo group (breast cancer [2 subjects]; lung neoplasm malignant [1 subject]), 3.6% (2 of 56) of subjects in the 0.1 mg group (small cell lung cancer metastatic; and lung neoplasm malignant, 1 subject each), and 3.6% (2 of 56) of subjects in the 0.4 mg group (bile duct cancer; and lung neoplasm malignant, 1 subject each), but a causal relationship to study drug was ruled out for all these cases. The incidences of non-fatal serious adverse events were 5.4% (3 of 56 subjects) in the placebo group (toxic skin eruption; febrile neutropenia; and ileus and pneumonia, 1 subject each), 5.4% (3 of 56 subjects) in the 0.1 mg group (gastrointestinal haemorrhage; febrile neutropenia; and delirium, 1 subject each), 6.9% (4 of 58 subjects) in the 0.2 mg group (delirium; pneumonia and pyrexia; idiopathic thrombocytopenic purpura; and interstitial lung disease, 1 subject each), and 10.7% (6 of 56 subjects) in the 0.4 mg group (pneumonia; anaemia; asthenia; vena cava thrombosis; ileus; and jaundice cholestatic, 1 subject each). A causal relationship to study drug could not be ruled out for gastrointestinal haemorrhage reported by 1 subject in the 0.1 mg group, but the event resolved following treatment discontinuation. The incidences of adverse events leading to treatment discontinuation other than fatal and non-fatal serious adverse events were 1.8% (1 of 56 subjects) in the placebo

group (gait disturbance), 3.6% (2 of 56 subjects) in the 0.1 mg group (abdominal pain and diarrhoea; and diarrhoea, 1 subject each), 1.7% (1 of 56 subjects) in the 0.2 mg group (diarrhoea), and 5.4% (3 of 56 subjects) in the 0.4 mg group (diarrhoea [2 subjects]; abdominal pain and diarrhoea [1 subject]). A causal relationship to study drug could not be ruled out for abdominal pain and diarrhoea; and diarrhoea occurring in the 0.1 mg group, diarrhoea reported by 1 subject in the 0.2 mg group, and diarrhoea reported by 2 subjects and abdominal pain and diarrhoea reported by 1 subject in the 0.4 mg group, but all these events resolved following treatment discontinuation.

7.2 Phase III studies

7.2.1 Japanese phase III study in patients with cancer (CTD 5.3.5.1-02, Study ID 1331V9236 [20 to 20], "Study V9236")

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 70 sites in Japan to evaluate the efficacy and safety of naldemedine in Japanese patients with cancer and OIC who were aged ≥20 years (Table 36) (target sample size, 190 subjects [95 per group]).

Placebo or naldemedine 0.2 mg was administered orally once daily for 14 days. Patients receiving regular laxative agents at the time of enrollment were required to maintain the laxative regimen. Dose reduction of regular opioids, changes in dosage regimen, or changes of drug or dosage form were not allowed. (However, dose increase was permitted if considered necessary by the investigator due to increased pain, and use of rescue opioid was allowed in the event of sudden pain.)

In total, 193 randomized subjects (96 in the placebo group, 97 in the naldemedine 0.2 mg group) were included in the FAS and in the safety analysis population; the FAS was used as the primary efficacy analysis population. There were 22 withdrawals (8 in the placebo group, 14 in the naldemedine 0.2 mg group), and the reasons for withdrawals were adverse events (11 subjects [1 in the placebo group, 10 in the naldemedine 0.2 mg group]), patient's request (2 subjects [1 each in the placebo and naldemedine 0.2 mg groups]), ineligibility (1 in the placebo group), lack of efficacy/worsening (1 in the placebo group), and others (7 subjects [4 in the placebo group, 3 in the naldemedine 0.2 mg group]).

The primary efficacy endpoint was the SBM responder rate during the 2-week treatment period (the proportion of patients with ≥3 SBMs per week and an increase of ≥1 SBM per week from baseline) (for results, see Table 40). A statistically significant difference was observed between the naldemedine and placebo groups ($P < 0.0001$, χ^2 test, two-sided significance level of 5%).

Table 40. SBM responder rates during 2-week treatment period (FAS)

	Placebo (N = 96)	Naldemedine 0.2 mg (N = 97)
SBM responder rate	34.4% (33/96)	71.1% (69/97)
Treatment difference (Naldemedine − Placebo) [95% CI][a)]	36.8% [23.7, 49.9]	
P-value[b)]	< 0.0001	

a) Clopper-Pearson method
b) $\chi 2$ test, Two-sided significance level of 5%

The incidences of adverse events were 35.4% (34 of 96 subjects) in the placebo group and 55.7% (54 of 97 subjects) in the naldemedine 0.2 mg group. The incidences of adverse drug reactions were 10.4% (10 of 96 subjects) in the placebo group and 21.6% (21 of 97 subjects) in the naldemedine 0.2 mg group. Adverse events and adverse drug reactions occurring in ≥2.0% of subjects in either group are shown in Table 41 and Table 42, respectively.

Table 41. Adverse events occurring in ≥2.0% of subjects in either group

	Placebo (N = 96)	Naldemedine 0.2 mg (N = 97)		Placebo (N = 96)	Naldemedine 0.2 mg (N = 97)
Any adverse event	35.4 (34)	55.7 (54)	Pneumonia bacterial	0 (0)	2.1 (2)
Diarrhoea	7.3 (7)	19.6 (19)	Pancytopenia	0 (0)	2.1 (2)
Vomiting	2.1 (2)	4.1 (4)	Thrombocytopenia	0 (0)	2.1 (2)
Pyrexia	2.1 (2)	4.1 (4)	Epistaxis	0 (0)	2.1 (2)
Malaise	1.0 (1)	4.1 (4)	Hyperhidrosis	0 (0)	2.1 (2)
White blood cell count decreased	0 (0)	4.1 (4)	Contusion	0 (0)	2.1 (2)
Nausea	4.2 (4)	3.1 (3)	Lung neoplasm malignant	3.1 (3)	1.0 (1)
Anaemia	2.1 (2)	3.1 (3)	Neutropenia	3.1 (3)	1.0 (1)
Fall	1.0 (1)	3.1 (3)	Nasopharyngitis	2.1 (2)	1.0 (1)
Decreased appetite	0 (0)	3.1 (3)	Insomnia	2.1 (2)	1.0 (1)
Somnolence	1.0 (1)	2.1 (2)	Pneumonia	4.2 (4)	0 (0)
Abdominal pain	1.0 (1)	2.1 (2)	Platelet count decreased	3.1 (3)	0 (0)
Stomatitis	1.0 (1)	2.1 (2)			

MedDRA/J ver.16.1; Incidence % (n)

Table 42. Adverse drug reactions occurring in ≥2.0% of subjects in either group

	Placebo (N = 96)	Naldemedine 0.2 mg (N = 97)
Any adverse drug reaction	10.4 (10)	21.6 (21)
Diarrhoea	5.2 (5)	17.5 (17)
Abdominal pain	1.0 (1)	2.1 (2)
Vomiting	1.0 (1)	2.1 (2)

MedDRA/J ver.16.1; Incidence % (n)

Deaths occurred in 4.2% (4 of 96) of subjects in the placebo group (lung neoplasm malignant [3 subjects]; phyllodes tumour [1 subject]) and 3.1% (3 of 97) of subjects in the naldemedine 0.2 mg group (pneumonia influenzal and pneumonia bacterial; lung neoplasm malignant; and interstitial lung disease, 1 subject each), but a causal relationship to study drug was ruled out for all these cases. The incidences of non-fatal serious adverse

events were 7.3% (7 of 96 subjects) in the placebo group (pneumonia [2 subjects]; radiation pneumonitis; pneumonia pneumococcal and sepsis; pelvic fracture; infection; and febrile neutropenia, 1 subject each) and 7.2% (7 of 97 subjects) in the naldemedine 0.2 mg group (diarrhoea, vomiting, and liver function test abnormal; asthenia and malaise; diarrhoea; gastroenteritis norovirus; pancytopenia; dizziness; and femur fracture, 1 subject each). Although a causal relationship to study drug could not be ruled out for pneumonia reported by 1 subject in the placebo group, and diarrhoea, vomiting, and liver function test abnormal reported by 1 subject and diarrhoea reported by 1 subject in the naldemedine 0.2 mg group, the outcomes of these events were all reported as "resolved." The incidences of adverse events leading to treatment discontinuation other than fatal and non-fatal serious adverse events were 1.0% (1 of 96 subjects) in the placebo group (somnolence) and 5.2% (5 of 97 subjects) in the naldemedine 0.2 mg group (diarrhoea [2 subjects]; pyrexia; vomiting; and diarrhoea, decreased appetite, and hyperhidrosis, 1 subject each). A causal relationship to study drug could not be ruled out for diarrhoea reported by 2 subjects, pyrexia reported by 1 subject, vomiting reported by 1 subject, and diarrhoea and decreased appetite reported by 1 subject in the naldemedine 0.2 mg group, but all these events resolved following treatment discontinuation.

7.2.2 Japanese phase III extension study in patients with cancer (CTD 5.3.5.2-01, Study ID 1332V9237 [[redacted] to [redacted]], "Study V9237")

A multicenter, open-label, uncontrolled study was conducted at 70 sites in Japan to evaluate the safety and efficacy of naldemedine in Japanese patients with cancer and OIC who completed Study V9236 (target sample size, 100 subjects).

Naldemedine 0.2 mg was administered orally once daily for 12 weeks. If subjects were suspected to have decreased QOL due to adverse events such as diarrhoea, dose reduction to 0.1 mg was permitted. At Week 2 and thereafter, if considered appropriate by the investigator, regular laxative agents were discontinued as a rule, and if bowel movements did not occur as expected, regular laxatives agents were resumed.

Of 193 randomized subjects in Study V9236, 131 (69 in the placebo group, 62 in the naldemedine 0.2 mg group) were enrolled in this study. All of the 131 subjects were included in the FAS and in the safety analysis population, and the FAS was used as the efficacy analysis population.

As for efficacy, the changes in PAC-SYM and PAC-QOL scores (Table 34) from baseline (start of treatment in Study V9236) to last observation are shown in Table 43 and Table 44, respectively. Both overall scores and scores for individual domains improved from baseline.

Table 43. Change in PAC-SYM score from baseline to last observation (FAS)

	Abdominal symptoms	Rectal symptoms	Stool symptoms	Overall score
Score at baseline	1.03 ± 0.64 (n = 131)	0.66 ± 0.68 (n = 131)	1.48 ± 0.84 (n = 131)	1.13 ± 0.58 (n = 131)
Score at last observation	0.76 ± 0.73 (n = 119)	0.39 ± 0.55 (n = 119)	0.91 ± 0.70 (n = 119)	0.73 ± 0.52 (n = 119)
Change from baseline to last observation	-0.30 ± 0.71 (n = 119)	-0.28 ± 0.72 (n = 119)	-0.60 ± 0.86 (n = 119)	-0.42 ± 0.54 (n = 119)

Mean ± SD

Table 44. Change in PAC-QOL score from baseline to last observation (FAS)

	Physical discomfort	Psychological discomfort	Worries and concerns	Dissatisfaction	Overall score
Score at baseline	1.13 ± 0.66 (n = 131)	0.66 ± 0.54 (n = 131)	1.16 ± 0.73 (n = 131)	2.62 ± 0.72 (n = 131)	1.27 ± 0.54 (n = 131)
Score at last observation	0.66 ± 0.66 (n = 119)	0.37 ± 0.51 (n = 119)	0.80 ± 0.65 (n = 119)	2.00 ± 0.96 (n = 119)	0.87 ± 0.55 (n = 119)
Change from baseline to last observation	-0.48 ± 0.72 (n = 119)	-0.29 ± 0.60 (n = 119)	-0.36 ± 0.66 (n = 119)	-0.60 ± 1.04 (n = 119)	-0.40 ± 0.56 (n = 119)

Mean ± SD

The incidence of adverse events was 80.2% (105 of 131 subjects), and adverse events occurring in ≥2.0% of subjects are shown in Table 45. The incidence of adverse drug reactions was 15.3% (20 of 131 subjects), and diarrhoea was the only adverse drug reaction occurring in ≥2.0% of subjects (9.2% [12 of 131 subjects]).

Table 45. Adverse events occurring in ≥2.0% of naldemedine-treated subjects

	Naldemedine 0.2 mg (N = 131)		Naldemedine 0.2 mg (N = 131)
Any adverse event	80.2 (105)	Paronychia	3.1 (4)
Diarrhoea	18.3 (24)	Febrile neutropenia	3.1 (4)
Nausea	13.0 (17)	Neutropenia	3.1 (4)
Vomiting	12.2 (16)	Hyperkalaemia	3.1 (4)
Decreased appetite	10.7 (14)	Delirium	3.1 (4)
Malaise	9.9 (13)	Somnolence	3.1 (4)
Nasopharyngitis	6.9 (9)	Epistaxis	3.1 (4)
Anaemia	6.1 (8)	Dry skin	3.1 (4)
Insomnia	5.3 (7)	Pruritus	3.1 (4)
Pneumonia	4.6 (6)	Cystitis	2.3 (3)
Stomatitis	4.6 (6)	Lung neoplasm malignant	2.3 (3)
Oedema peripheral	4.6 (6)	Thrombocytopenia	2.3 (3)
Headache	3.8 (5)	Hypoaesthesia	2.3 (3)
Rash	3.8 (5)	Abdominal pain	2.3 (3)
Back pain	3.8 (5)	Abdominal pain upper	2.3 (3)
Pyrexia	3.8 (5)	Decubitus ulcer	2.3 (3)

MedDRA/J ver.16.1; Incidence % (n)

Deaths occurred in 11.5% (15 of 131) of subjects (pancreatic carcinoma; and lung neoplasm malignant [2 subjects each]; lung adenocarcinoma; pneumonia and lung neoplasm malignant; malignant neoplasm of pleura and chronic obstructive pulmonary disease; inflammatory carcinoma of the breast; pleural mesothelioma malignant; prostate cancer; breast cancer; non-small cell lung cancer; malignant neoplasm of unknown primary site; metastases to meninges; and gastric cancer, 1 subject each), but a causal relationship to naldemedine was ruled out for all these cases. The incidence of non-fatal serious adverse events was 10.7% (14 of 131 subjects) (depression; cardiac failure; ileus; urinary tract infection; hepatic function abnormal; gastroenteritis; liver injury, pneumonia, and chronic myelomonocytic leukaemia; pneumonia; febrile neutropenia; anaemia; pneumonia pneumococcal and lower respiratory tract inflammation; pneumonia bacterial; deep vein thrombosis and epistaxis; and venous thrombosis limb, decreased appetite, infection, and delirium, 1 subject each), but a causal relationship to naldemedine was ruled out for all these events. The incidence of adverse events leading to treatment discontinuation other than fatal and non-fatal serious adverse events was 3.1% (4 of 131 subjects) (diarrhoea [2 subjects]; abdominal pain upper and diarrhoea; and blood creatinine increased,

1 subject each). Although a causal relationship to naldemedine could not be ruled out except for abdominal pain upper, all these events resolved following treatment discontinuation.

7.2.3 Japanese long-term treatment study in patients with chronic non-cancer pain (CTD 5.3.5.2-02, Study ID 1336V9238 [[redacted] to [redacted]], "Study V9238")

A multicenter, open-label, uncontrolled study was conducted at 21 sites in Japan to evaluate the long-term safety and efficacy of naldemedine in Japanese patients with OIC and chronic non-cancer pain who were aged ≥20 years (Table 46) (target sample size, 40 subjects).

Table 46. Key inclusion criteria for patients with OIC and chronic non-cancer pain

● Chronic pain for ≥3 months, and a diagnosis of chronic non-cancer pain
● Regular opioid use for ≥2 weeks, and a stable opioid regimen for 14 days prior to formal enrollment
● ≤5 SBMs with ≥1 of the following symptoms in ≥25% of BMs during 14 days prior to formal enrollment:
・Straining (Straining score ≥2 [moderate])
・Feeling of incomplete evacuation
・Hard or lumpy stools (BSS [Table 35] 1 or 2)

Naldemedine 0.2 mg was administered orally once daily for 48 weeks. At Week 3 and thereafter, naldemedine interruption (for up to 2 weeks) and dose reduction to 0.1 mg were permitted if a patient was suspected to have decreased QOL due to adverse events such as diarrhoea. Patients receiving regular laxative agents at the time of enrollment were required to maintain the laxative regimen during the first 2 weeks of the treatment period. At Week 3 and thereafter, if considered appropriate by the investigator, regular laxative agents were discontinued as a rule, and if bowel movements did not occur as expected, regular laxatives agents were resumed. If opioid therapy was interrupted, naldemedine also was interrupted. Once opioid therapy was resumed, naldemedine also was resumed.

All 43 subjects enrolled in this study were included in the safety analysis population. Excluding 1 subject with no efficacy endpoint data, 42 subjects were included in the FAS, and the FAS was used as the primary efficacy analysis population. There were 12 withdrawals for the following reasons: patient's request (7 subjects), adverse events (3 subjects), ineligibility (1 subject), and lack of efficacy/worsening (1 subject).

As for efficacy, the SBM responder rate during the first 2 weeks of the treatment period was 81.0% (34 of 42 subjects).

The incidence of adverse events was 88.4% (38 of 43 subjects), and adverse events occurring in ≥2 subjects are shown in Table 47. The incidence of adverse drug reactions was 27.9% (12 of 43 subjects), and adverse drug reactions occurring in ≥2 subjects were diarrhoea (14.0% [6 of 43 subjects]) and abdominal pain (7.0% [3 of 43 subjects]).

Table 47. Adverse events occurring in ≥2 naldemedine-treated subjects

	Naldemedine 0.2 mg (N = 43)		Naldemedine 0.2 mg (N = 43)
Any adverse event	88.4 (38)	Gastroenteritis	4.7 (2)
Nasopharyngitis	25.6 (11)	Influenza	4.7 (2)
Diarrhoea	23.3 (10)	Anxiety	4.7 (2)
Nausea	11.6 (5)	Dizziness	4.7 (2)
Abdominal pain	9.3 (4)	Eczema	4.7 (2)
Vomiting	9.3 (4)	Blood CPK increased	4.7 (2)
Decreased appetite	7.0 (3)	Fall	4.7 (2)
Somnolence	7.0 (3)	Ligament sprain	4.7 (2)
Contusion	7.0 (3)		

MedDRA/J ver.16.1; Incidence % (n)

Death occurred in 2.3% (1 of 43) of subjects (sudden death[14]), but its causal relationship to naldemedine was ruled out. The incidence of serious adverse events was 9.3% (4 of 43 subjects [urethral stenosis; cerebral infarction and cholelithiasis; ileus; and urinary tract infection, 1 subject each]), but a causal relationship to naldemedine was ruled out for all these events. The incidence of adverse events leading to treatment discontinuation, other than fatal and non-fatal serious adverse events, was 2.3% (1 of 43 subjects [anal fissure]), but its causal relationship to naldemedine was ruled out.

7.2.4 Study in patients with chronic non-cancer pain receiving oxycodone hydrochloride (CTD 5.3.5.2-03, Study ID 1339V9239 [[redacted] to [redacted]], "Study V9239")

A multicenter, open-label, uncontrolled study was conducted at 9 sites in Japan to evaluate the long-term safety and efficacy of naldemedine in Japanese patients with OIC and chronic non-cancer pain receiving oxycodone hydrochloride who were aged ≥20 and <80 years (Table 48) (target sample size, 10 subjects).

Table 48. Key inclusion criteria for patients with OIC and chronic non-cancer pain

- **Chronic pain for ≥3 months and a diagnosis of chronic non-cancer pain, with either of the following conditions.**
  - **BPI-pain severity score (average pain) ≥4 during 24 hours prior to tentative enrollment in patients who have been on non-opioid analgesics, oral tramadol, oral codeine (≤800 mg/day), or buprenorphine patch for ≥14 days.**
  - **Patients who have been on oral morphine (≤ 120 mg/day) or fentanyl patch (≤100 μg/hour) for ≥14 days (regardless of BPI-pain severity).**
- **A stable regimen of oxycodone hydrochloride for 14 days prior to formal enrollment**
- **≤5 SBMs with ≥1 of the following symptoms in ≥25% of BMs during 14 days prior to formal enrollment:**
  - **Straining (Straining score ≥2 [moderate])**
  - **Feeling of incomplete evacuation**
  - **Hard or lumpy stools (BSS [Table 35] 1 or 2)**

Naldemedine 0.2 mg was administered orally once daily for 48 weeks. At Week 3 and thereafter, naldemedine interruption (for up to 2 weeks) and dose reduction to 0.1 mg were permitted if a patient was suspected to have decreased QOL due to adverse events such as diarrhoea. Patients receiving regular laxative agents at the time of enrollment were required to maintain the laxative regimen during the first 2 weeks of the treatment period. At Week 3 and thereafter, if considered appropriate by the investigator, regular laxative agents were discontinued as a rule, and if bowel movements did not occur as expected, regular laxative agents were resumed. If oxycodone hydrochloride was interrupted, naldemedine also was interrupted. Once oxycodone hydrochloride was resumed, naldemedine also was resumed.

[14] Although the cause of death could not be identified, its causal relationship to naldemedine was ruled out by the investigator because of the patient's prior history (lower limb venous thrombosis and pulmonary embolism) and the mechanism of action of naldemedine.

All 10 subjects enrolled in this study were included in the FAS and in the safety analysis population, and the FAS was used as the primary efficacy analysis population. There were 3 withdrawals, and the reasons for withdrawals were adverse events (2 subjects) and patient's request (1 subject).

As for efficacy, the SBM responder rate during the first 2 weeks of the treatment period was 90.0% (9 of 10 subjects).

The incidence of adverse events was 90.0% (9 of 10 subjects), and adverse events occurring in ≥2 subjects were diarrhoea (40.0% [4 of 10 subjects]), nasopharyngitis (30.0% [3 of 10 subjects]), anxiety (20.0% [2 of 10 subjects]), and malaise (20.0% [2 of 10 subjects]). The incidence of adverse drug reactions was 50.0% (5 of 10 subjects), and adverse drug reactions occurring in ≥2 subjects were diarrhoea (40.0% [4 of 10 subjects]). There were no deaths or serious adverse events. An adverse event (malaise) led to treatment discontinuation, (10.0% [1 of 10 subjects]); the event resolved following treatment discontinuation, and its causal relationship to naldemedine was ruled out.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

PMDA's view:

Based on the following considerations and confirmation described in Sections 7.R.1.1 to 7.R.1.5, naldemedine has been shown to be effective in the treatment of OIC. However, only limited information is available on the efficacy of naldemedine in Japanese patients with chronic non-cancer pain and on the long-term persistence of the effectiveness of naldemedine. Information should therefore be collected via post-marketing surveillance etc.

A final conclusion on the efficacy of naldemedine will be made, taking account of comments from the Expert Discussion.

7.R.1.1 Efficacy in patients with cancer

7.R.1.1.1 Primary endpoint

The applicant's explanation on the rationale for the selected primary endpoint and treatment duration for studies in patients with cancer:

The change in weekly frequency of SBMs from baseline to the 2-week treatment period, was selected as the primary endpoint for a multi-regional (Japan and Korea) phase II study in patients with cancer (Study V9222), in order to assess changes in frequency of BMs in patients. A 2-week treatment period was selected, because patients with cancer might experience worsening of their disease due to progression of cancer, and because an expert commented that although the initiation and change of cancer chemotherapy may affect efficacy evaluation, the use of cancer chemotherapy can be restricted for as short as 2 weeks.

Table 37 shows the change from baseline in weekly frequency of SBMs during the 2-week treatment period in the multi-regional (Japan and Korea) phase II study in patients with cancer (Study V9222). The superiority of naldemedine 0.1, 0.2, and 0.4 mg over placebo was demonstrated in both populations. In this multi-regional phase II study, a total of 226 subjects were treated, of whom 214 subjects (94.7%) were Japanese.

The primary endpoint of the multi-regional phase II study (Study V9222) was the change from baseline in weekly frequency of SBMs during the 2-week treatment period. This endpoint clearly detects changes in frequency of BMs in patients. However, if some patients experience a marked increase in frequency of BMs, averaged data may complicate the interpretation of overall results. Hence, in a Japanese phase III study (Study V9236), the proportion of responders (defined as patients with a certain level of improvement in constipation) in the naldemedine and placebo groups were compared, because this would allow more appropriate evaluation of the efficacy of naldemedine as an anti-constipating agent. In order to assess the improvement in constipation, an SBM responder was defined as a patient with ≥3 SBMs per week and an increase of ≥1 SBM per week from baseline. This definition was based on Rome III diagnostic criteria for functional constipation, because the diagnostic criteria for OIC had not been established at the time of development of naldemedine. Taking account of these points, the SBM responder rate during the 2-week treatment period was selected as the primary endpoint for the Japanese phase III study (Study V9236).

The Japanese phase III study (Study V9236) demonstrated the superiority of naldemedine 0.2 mg over placebo in the SBM responder rate during the 2-week treatment period (Table 40).

Based on the above, naldemedine has been shown to be effective in the treatment of OIC in patients with cancer.

PMDA's view:
It is understandable that the SBM responder rate during the 2-week treatment period was selected as the primary endpoint for the Japanese phase III study (Study V9236), based on the diagnostic criteria for functional constipation with similar clinical symptoms, because the diagnostic criteria for OIC had not been established at the time of development.

The Japanese phase III study (Study V9236) showed the superiority of naldemedine 0.2 mg over placebo, demonstrating the efficacy of naldemedine in the treatment of OIC in patients with cancer.

7.R.1.1.2 Key secondary endpoints

A Japanese phase III study (Study V9236) evaluated the secondary endpoints of the CSBM responder rate during the 2-week treatment period, the time to the first SBM, the PAC-SYM responder rate,[15)] the PAC-QOL responder rate,[16)] etc. (for results, see Table 49). Naldemedine tended to be more effective than placebo across all endpoints.

[15)] The proportion of patients with a ≥1-point decrease from baseline in mean overall PAC-SYM score
[16)] The proportion of patients with a ≥1-point decrease from baseline in mean PAC-QOL dissatisfaction score

Table 49. Results of key secondary endpoints (Study V9236, FAS)

	Placebo (N = 96)	Naldemedine 0.2 mg (N = 97)
CSBM responder rates during 2-week treatment period	12.5% (12/96)	40.2% (39/97)
Treatment difference (Naldemedine − Placebo) [95% CI]	27.7% [15.9, 39.5]	
Time to first SBM (Median [95% CI])[a)]	26.58 h [19.65, 58.17]	4.67 h [3.00, 7.58]
PAC-SYM responder rates at last observation	3.2% (3/95)	10.8% (10/93)
Treatment difference (Naldemedine − Placebo) [95% CI]	7.6% [0.4, 14.8]	
PAC-QOL responder rates at last observation	18.9% (18/95)	31.2% (29/93)
Treatment difference (Naldemedine − Placebo) [95% CI]	12.2% [0.0, 24.5]	

a) Median and its 95% confidence interval are based on Kaplan-Meier estimates of time to first SBM

7.R.1.2 Efficacy in patients with chronic non-cancer pain

The applicant's explanation on the efficacy of naldemedine in patients with chronic non-cancer pain:
Since the number of patients with chronic non-cancer pain is limited in Japan, it is difficult to conduct a comparative study. Thus, an uncontrolled study was conducted.

In Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239), the SBM responder rates during the first 2 weeks of the treatment period were 81.0% in Study V9238 and 90.0% in Study V9239. These responder rates were non-inferior to that in Study V9236 in patients with cancer.

Opioids have been more wildly used in foreign countries than in Japan for the treatment of chronic non-cancer pain; in foreign countries, double-blind comparative studies have been conducted in patients with chronic non-cancer pain (Studies V9231[17)] and V9232[18)]). Table 50 shows the SBM responder rates during the 12-week treatment period (the proportion of patients with ≥3 SBMs per week and an increase of ≥1 SBM per week from baseline for ≥9 out of the 12-week treatment period and for ≥3 out of the last 4 weeks of the 12-week treatment period) in these studies. These results demonstrate the efficacy of naldemedine 0.2 mg compared with placebo.

Table 50. SBM responder rates during 12-week treatment period (Foreign phase III studies [Studies V9231 and V9232], FAS)

	Placebo	Naldemedine 0.2 mg
Study V9231		
N	272	273
SBM responder rate	34.6% (94/272)	47.6% (130/273)
Treatment difference (Naldemedine − Placebo) [95% CI]	13.0% [4.8, 21.3]	
Study V9232		
N	274	276
SBM responder rate	33.6% (92/274)	52.5% (145/276)
Treatment difference (Naldemedine − Placebo) [95% CI]	18.9% [10.8, 27.0]	

17) A multicenter, randomized, double-blind, placebo-controlled, parallel-group study in 547 patients with OIC and chronic non-cancer pain who were aged between 18 and 80 years (273 in the placebo group, 274 in the naldemedine 0.2 mg group) to demonstrate the superiority of naldemedine over placebo. Naldemedine 0.2 mg was administered orally once daily for 12 weeks.

18) A multicenter, randomized, double-blind, placebo-controlled, parallel-group study in 553 patients with OIC and chronic non-cancer pain who were aged between 18 and 80 years (276 in the placebo group, 277 in the naldemedine 0.2 mg group) to demonstrate the superiority of naldemedine over placebo. Naldemedine 0.2 mg was administered orally once daily for 12 weeks.

PMDA's view:

There were no relevant differences in “the SBM responder rate during the 2-week treatment period with naldemedine 0.2 mg” between the Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239) and the Japanese phase III study in patients with cancer (Study V9236). The foreign phase III studies in patients with chronic non-cancer pain (Studies V9231 and V9232) demonstrated the efficacy of naldemedine compared with placebo. These findings suggest the efficacy of naldemedine in patients with chronic non-cancer pain. However, since the number of Japanese patients with chronic non-cancer pain enrolled in clinical studies was limited, information should be collected via post-marketing surveillance etc.

7.R.1.3 Long-term efficacy

The applicant's explanation on the rationale for the treatment duration (12 weeks) for an extension study in patients with cancer:

How opioid analgesics were actually used in routine clinical settings suggested that even patients with cancer were expected to receive opioid analgesics for ≥3 months in clinical practice. Thus, the applicant decided to conduct an extension study (Study V9237) of a Japanese phase III study (Study V9236) to evaluate the efficacy of naldemedine administered for 12 weeks in patients with cancer.

The SBM responder rate was used as the primary efficacy endpoint for the Japanese phase III study (Study V9236). In the extension study (Study V9237), the PAC-SYM responder rate was used for efficacy evaluation instead of the frequency of SBs. In the extension study, the frequency of SBMs could not be used for efficacy evaluation because the enrolled patients with cancer were treated with naldemedine for a long period of time and therefore were allowed to receive concomitant antineoplastics, surgical therapy, procedures, and radiation therapy that affect the gastrointestinal function. The PAC-SYM responder rates at different time points are presented in Table 51, showing a trend towards improvement from baseline (start of treatment in Study V9236) at all time points.

Table 51. PAC-SYM responder rates at different time points (Study V9237, FAS)

Naldemedine 0.2mg (N = 52)	Week 0	Week 2	Week 4	Week 8	Week 12	Last observation
Responder rate	5.3% (7/131)	22.0% (28/127)	15.8% (19/120)	16.8% (19/113)	15.2% (16/105)	18.5% (22/119)

Table 52 shows the PAC-SYM responder rates at different time points, based on pooled data from Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239). The results show a trend towards improvement from baseline (start of treatment in Studies V9238 and V9239) at all time points, as with the trend in patients with cancer.

Table 52. PAC-SYM responder rates at different time points (Pooled data from Studies V9238 and V9239, FAS)

Naldemedine 0.2mg (N = 52)	Week 2	Week 12	Week 24	Week 36	Week 48	Last observation
Responder rate	27.5% (14/51)	35.6% (16/45)	45.2% (19/42)	45.0% (18/40)	47.4% (18/38)	42.0% (21/50)

PMDA's view:

The PAC-SYM responder rate, as measured by patient assessment of constipation symptoms, tended to improve from baseline to Week 2 and thereafter in both patients with cancer and patients with chronic non-cancer pain, showing no trend towards decreasing effectiveness with prolonged treatment. However, as the number of patients treated with naldemedine for a long period of time was limited, information on the long-term efficacy of naldemedine should continue to be collected via post-marketing surveillance.

7.R.1.4 Efficacy by patient characteristics

Table 53 shows the SBM responder rates during the 2-week treatment period by patient characteristics, based on pooled data from Japanese studies in patients with cancer (Studies V9222 and V9236) and pooled data from Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239). The SBM responder rate during the 2-week treatment period tended to be higher in the naldemedine group than in the placebo group across all subgroups of patients with cancer. A similar trend was observed also in patients with chronic non-cancer pain.

Table 53. SBM responder rates during 2-week treatment period by patient characteristics (Pooled data from studies in patients with cancer [Studies V9222 and V9236]) and pooled data from studies in patients with chronic non-cancer pain [Studies V9238 and V9239])

Patient characteristics	Subgroup	Patients with cancer (V9222 + V9236)		Patients with chronic non-cancer pain (V9238 + V9239)
		Placebo (N = 152)	Naldemedine (N = 155)	Naldemedine (N = 52)
Sex	Male	34.0 (32/94)	68.8 (64/93)	95.2 (20/21)
	Female	37.9 (22/58)	80.6 (50/62)	74.2 (23/31)
Age	< 65 years	36.6 (26/71)	79.7 (63/79)	78.3 (18/23)
	≥ 65 years	34.6 (28/81)	67.1 (51/76)	86.2 (25/29)
Opioid type	Oxycodone hydrochloride	31.4 (32/102)	75.9 (82/108)	90.0 (9/10)
	Fentanyl citrate	44.4 (16/36)	73.3 (22/30)	75.0 (21/28)
	Morphine hydrochloride	47.1 (8/17)	66.7 (10/15)	88.9 (8/9)
	Others	0 (0/1)	50.0 (4/8)	73.3 (11/15)
Regular opioid dose at baseline (oral morphine equivalent)	<60 mg/day	38.8 (33/85)	72.8 (59/81)	87.5 (21/24)
	≥60 mg/day	31.3 (21/67)	74.3 (55/74)	78.6 (22/28)
Regular laxative use	Yes	38.5 (50/130)	73.8 (96/130)	80.9 (38/47)
	No	18.2 (4/22)	72.0 (18/25)	100 (5/5)
Regular laxative type	Magnesium oxide	41.9 (49/117)	73.3 (85/116)	82.1 (32/39)
	Sennoside	43.5 (10/23)	71.4 (15/21)	75.0 (9/12)
	Others	31.8 (7/22)	70.0 (14/20)	69.2 (9/13)

SBM responder rate % (No. of responders/No. of evaluable subjects)

7.R.2 Safety

Based on the following considerations described in Sections 7.R.2.1 to 7.R.2.4, PMDA considers that the safety of naldemedine is acceptable. However, it is necessary to continue to collect information on diarrhoea, gastrointestinal perforation, cardiovascular events, opioid withdrawal syndrome, and effects on opioid analgesia via post-marketing surveillance etc. Since the number of patients receiving long-term treatment with naldemedine is limited, information on the long-term safety of naldemedine should be collected via post-marketing surveillance etc.

A final conclusion on the safety of naldemedine will be made, taking account of comments from the Expert Discussion.

7.R.2.1 Safety in patients with cancer

Table 54 shows the incidence of adverse events based on pooled data from a multi-regional (Japan and Korea) study (Study V9222) and a Japanese phase III study (Study V9236) in patients with cancer. The incidences of diarrhoea and decreased appetite tended to be higher in the naldemedine 0.2 mg group than in the placebo group. The events of decreased appetite occurring in 9 subjects in the naldemedine 0.2 mg group were all mild or moderate in severity. The incidences of adverse drug reactions were 21.1% (32 of 152 subjects) in the placebo group and 31.0% (48 of 155 subjects) in the naldemedine 0.2 mg group. Adverse drug reactions occurring in ≥2.0% of subjects in either group were diarrhoea (11.8% [18 of 152 subjects] in the placebo group, 24.5% [38 of 155 subjects] in the naldemedine 0.2 mg group) and nausea (2.0% [3 of 152 subjects] in the placebo group, 0.6% [1 of 155 subjects] in the naldemedine 0.2 mg group).

Table 54. Adverse events occurring in ≥2.0% of subjects in either group (Pooled data from studies in patients with cancer [Studies V9222 and V9236])

	Placebo (N = 152)	Naldemedine 0.2 mg (N = 155)		Placebo (N = 152)	Naldemedine 0.2 mg (N = 155)
Adverse events	50.0 (76)	66.5 (103)	Abdominal pain	0.7 (1)	3.2 (5)
Adverse drug reactions	21.1 (32)	31.0 (48)	ALT increased	0.7 (1)	3.2 (5)
Deaths	4.6 (7)	1.9 (3)	Anaemia	3.3 (5)	2.6 (4)
Non-fatal serious adverse events	6.6 (10)	7.1 (11)	Nasopharyngitis	2.6 (4)	2.6 (4)
Adverse events leading to treatment discontinuation	1.3 (2)	7.1 (11)	Blood ALP increased	2.6 (4)	2.6 (4)
Diarrhoea	15.8 (24)	29.0 (45)	Protein urine present	1.3 (2)	2.6 (4)
White blood cell count decreased	5.3 (8)	6.5 (10)	GGT increased	2.6 (4)	1.9 (3)
Decreased appetite	1.3 (2)	5.8 (9)	Haemoglobin decreased	2.0 (3)	1.9 (3)
Nausea	5.9 (9)	4.5 (7)	Bone marrow failure	2.0 (3)	1.3 (2)
Malaise	1.3 (2)	4.5 (7)	Neutropenia	2.0 (3)	1.3 (2)
Protein total decreased	1.3 (2)	4.5 (7)	Pneumonia	3.3 (5)	0.6 (1)
Vomiting	1.3 (2)	3.9 (6)	Lung neoplasm malignant	2.6 (4)	0.6 (1)
Pyrexia	1.3 (2)	3.9 (6)	Dizziness	2.6 (4)	0.6 (1)
Blood urea increased	0.7 (1)	3.9 (6)	Platelets decreased	2.6 (4)	0.6 (1)
Somnolence	2.0 (3)	3.2 (5)	Haematocrit decreased	2.0 (3)	0.6 (1)
AST increased	1.3 (2)	3.2 (5)			

MedDRA/J ver.16.1; Incidence % (n)

Deaths occurred in 4.6% (7 of 152) of subjects in the placebo group (lung neoplasm malignant [4 subjects]; breast cancer [2 subjects]; phyllodes tumour [1 subject]) and 1.9% (3 of 155) of subjects in the naldemedine

0.2 mg group (lung neoplasm malignant; pneumonia influenzal and pneumonia bacterial; and interstitial lung disease, 1 subject each), but a causal relationship to study drug was ruled out for all these cases. The incidences of non-fatal serious adverse events were 6.6% (10 of 152 subjects) in the placebo group and 7.1% (11 of 155 subjects) in the naldemedine 0.2 mg group, showing no particular increase in incidence with naldemedine compared to placebo. The incidences of adverse events leading to treatment discontinuation were 1.3% (2 of 152 subjects) in the placebo group and 7.1% (11 of 155 subjects) in the naldemedine 0.2 mg group. The incidences of diarrhoea leading to treatment discontinuation were 0% (0 of 152 subjects) in the placebo group and 3.9% (6 of 155 subjects) in the naldemedine 0.2 mg group, showing a trend towards a higher incidence of diarrhoea leading to treatment discontinuation in the naldemedine 0.2 mg group compared to the placebo group. The incidence of diarrhoea tended to be higher in the naldemedine 0.2 mg group; the events of diarrhoea are discussed in Section 7.R.2.4.1.

7.R.2.2 Safety in patients with chronic non-cancer pain

Table 55 shows the incidence of adverse events based on pooled data from Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239). Although the incidences of nasopharyngitis, diarrhoea, and nausea tended to be high in subjects treated with 0.2 mg naldemedine, all these events, except for severe diarrhoea reported by 1 subject, were mild or moderate in severity.

Table 55. Adverse events occurring in ≥2.0% of naldemedine-treated subjects (Pooled data from studies in patients with chronic non-cancer pain [Studies V9238 and V9239])

	Naldemedine 0.2 mg (N = 53)		Naldemedine 0.2 mg (N = 53)
Adverse events	88.7 (47)	Malaise	5.7 (3)
Adverse drug reactions	32.1 (17)	Contusion	5.7 (3)
Deaths	1.9 (1)	Gastroenteritis	3.8 (2)
Non-fatal serious adverse events	7.5 (4)	Influenza	3.8 (2)
Adverse events leading to treatment discontinuation	7.5 (4)	Dizziness	3.8 (2)
Nasopharyngitis	26.4 (14)	Abdominal pain upper	3.8 (2)
Diarrhoea	26.4 (14)	Gastritis	3.8 (2)
Nausea	11.3 (6)	Eczema	3.8 (2)
Vomiting	9.4 (5)	Blood CPK increased	3.8 (2)
Anxiety	7.5 (4)	Protein urine present	3.8 (2)
Somnolence	7.5 (4)	Fall	3.8 (2)
Abdominal pain	7.5 (4)	Ligament sprain	3.8 (2)
Decreased appetite	5.7 (3)		

MedDRA/J ver.16.1; Incidence % (n)

Death occurred in 1.9% (1 of 53) of subjects (sudden death[13]), but its causal relationship to naldemedine was ruled out. The incidences of non-fatal serious adverse events and adverse events leading to treatment discontinuation were both 7.5% (4 of 53 subjects). None of these events occurred in ≥2 subjects, and a causal relationship to naldemedine was ruled out for all adverse events leading to treatment discontinuation.

PMDA confirmed that there were no clinically relevant adverse events in patients with chronic non-cancer pain. However, since the number of Japanese patients with chronic non-cancer pain enrolled in clinical studies was limited, information should be collected via post-marketing surveillance etc.

7.R.2.3 Long-term safety

Table 56 and Table 57 show the incidence of adverse events by timing of onset, based on pooled data from Japanese studies in patients with cancer (Studies V9222, V9236, and V9237) and pooled data from Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239). There was no increase in the incidence of adverse events with prolonged treatment in patients with cancer or chronic non-cancer pain.

Table 56. Incidence of adverse events by timing of onset in studies in patients with cancer (Pooled data from Studies V9222, V9236, and V9237)

Timing of onset (Day)	1-14	15-28	29-42	43-56	57-70	71-84	85-98	Entire treatment period[a)]
N	224	129	121	118	115	111	55	224
Adverse events	45.5 (102)	33.3 (43)	27.3 (33)	22.0 (26)	31.3 (36)	26.1 (29)	14.5 (8)	82.1 (184)
Adverse drug reactions	24.1 (54)	3.1 (4)	5.0 (6)	0.8 (1)	0 (0)	2.7 (3)	3.6 (2)	29.9 (67)
Serious adverse events [b)]	4.0 (9)	2.3 (3)	1.7 (2)	4.2 (5)	0.9 (1)	2.7 (3)	3.6 (2)	17.9 (40)
Adverse events leading to treatment discontinuation	5.8 (13)	1.6 (2)	0 (0)	0.8 (1)	0 (0)	0.9 (1)	0 (0)	10.7 (24)
Diarrhoea	22.3 (50)	3.9 (5)	1.7 (2)	0 (0)	0 (0)	3.6 (4)	1.8 (1)	30.4 (68)

MedDRA/J ver.16.1; Incidence % (n)
a) Including the follow-up period (4 weeks).
b) Including deaths.

Table 57. Incidence of adverse events by timing of onset in studies in patients with chronic non-cancer pain (Pooled data from Studies V9238 and V9239)

Timing of onset (Day)	1-28	29-56	57-84	85-112	113-140	141-168	169-196
N	53	49	48	45	43	42	42
Adverse events	47.2 (25)	22.4 (11)	22.9 (11)	33.3 (15)	27.9 (12)	21.4 (9)	16.7 (7)
Adverse drug reactions	30.2 (16)	2.0 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Serious adverse events [b)]	0 (0)	0 (0)	2.1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to treatment discontinuation	0 (0)	4.1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhoea	20.8 (11)	4.1 (2)	4.2 (2)	4.4 (2)	0 (0)	0 (0)	0 (0)

Timing of onset (Day)	197-224	225-252	253-280	281-308	309-336	Entire treatment period[a)]
N	42	41	40	40	38	53
Adverse events	16.7 (7)	24.4 (10)	20.0 (8)	20.0 (8)	0 (0)	88.7 (47)
Adverse drug reactions	0 (0)	0 (0)	0 (0)	2.5 (1)	0 (0)	32.1 (17)
Serious adverse events [b)]	0 (0)	0 (0)	5.0 (2)	0 (0)	0 (0)	9.4 (5)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7.5 (4)
Diarrhoea	0 (0)	2.4 (1)	0 (0)	2.5 (1)	0 (0)	26.4 (14)

MedDRA/J ver.16.1; Incidence % (n)
a) Including the follow-up period (2 weeks).
b) Including deaths.

7.R.2.4 Adverse events of special interest in patients receiving naldemedine

7.R.2.4.1 Diarrhoea

In Japanese studies in patients with cancer (Studies V9222, V9236, and V9237) and in patients with chronic non-cancer pain (Studies V9238 and V9239), diarrhoea was a common adverse event in naldemedine-treated subjects.

The applicant's explanation on the occurrence of diarrhoea associated with naldemedine:

Table 58 shows the incidence of diarrhoea in Japanese studies in patients with cancer or chronic non-cancer pain. Although the incidence of diarrhoea tended to be higher with naldemedine than with placebo, most of the events were mild or moderate in severity. In Japanese studies in patients with cancer (Studies V9222 and V9236), 1.3% (2 of 155) of subjects receiving naldemedine 0.2 mg had severe diarrhoea for which a causal relationship to naldemedine could not be ruled out, but these events resolved following treatment discontinuation. In an extension study in patients with cancer (Study V9237) and Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239), none of the subjects receiving 0.2 mg naldemedine had severe diarrhoea for which a causal relationship to naldemedine could not be ruled out.

Table 58. Incidence of adverse events of diarrhoea (Pooled data from studies in patients with cancer [Studies V9222, V9236, and V9237] and pooled data from studies in patients with chronic non-cancer pain [Studies V9238 and V9239])

	Patients with cancer			Patients with chronic non-cancer pain
	V9222 + V9236		V9237	V9238 + V9239
	Placebo (N = 152)	Naldemedine 0.2 mg (N = 155)	Naldemedine 0.2 mg (N = 131)	Naldemedine 0.2 mg (N = 53)
Total	15.8 (24)	29.0 (45)	18.3 (24)	26.4 (14)
Mild	15.1 (23)	27.1 (42)	13.7 (18)	13.2 (7)
Moderate	0.7 (1)	0.6 (1)	3.8 (5)	11.3 (6)
Severe	0 (0)	1.3 (2)	0.8 (1)	1.9 (1)

MedDRA/J ver.16.1; Incidence % (n)

PMDA's view:

The incidence of diarrhoea tended to be high in Japanese studies in patients with cancer or chronic non-cancer pain, but most of the events were mild or moderate in severity. Many of the diarrhoea events for which a causal relationship to naldemedine could not be ruled out resolved after appropriate action, such as treatment interruption, was taken. Thus, there are no clinically relevant problems at present. However, the package insert should contain a statement to the effect that if severe diarrhoea occurs during treatment with naldemedine, appropriate action such as treatment interruption should be taken.

7.R.2.4.2 Gastrointestinal perforation

In the US, fatal cases of gastrointestinal perforation associated with methylnaltrexone bromide have been reported (*J Pain Symptom Manage.* 2010; 40: e1-3, US labeling for Relistor). Methylnaltrexone bromide is another peripherally-acting μ-opioid receptor antagonist unapproved in Japan, and is indicated for patients with chronic non-cancer pain.

The applicant's explanation on the occurrence of gastrointestinal perforation associated with naldemedine:

In Japanese studies in patients with cancer (Studies V9222, V9236, and V9237), Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239), and foreign studies in patients with chronic non-cancer pain (Studies V9231, V9232, and V9235), gastrointestinal perforation-related events were analyzed. Gastrointestinal perforation-related events were defined as those coded to preferred terms under "gastrointestinal perforation (SMQ)" and "gastrointestinal perforation, ulcer, haemorrhage, obstruction non-specific findings/procedures (SMQ)."

No gastrointestinal perforation occurred in Japanese or foreign clinical studies.

In Japanese studies in patients with cancer (Studies V9222 and V9236), the incidences of gastrointestinal perforation-related events were 0.7% (1 of 152 subjects) in the placebo group (abdominal discomfort) and 1.3% (2 of 155 subjects) in the naldemedine 0.2 mg group (abdominal discomfort and enterocolitis in 1 subject each). In a Japanese extension study in patients with cancer (Study V9237), the incidence of gastrointestinal perforation-related events was 2.3% (3 of 131 subjects [abdominal discomfort in 2 subjects; enterocolitis in 1 subject]). All these events were mild or moderate in severity. No gastrointestinal perforation-related events occurred in Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239). In foreign studies in patients with chronic non-cancer pain (up to Week 12 in Studies V9231, V9232, and V9235), the incidences of gastrointestinal perforation-related events were 0.3% (4 of 1165 subjects) in the placebo group (abdominal discomfort in 2 subjects; gastrointestinal pain in 1 subject; and gastrointestinal sounds abnormal in 1 subject) and 0.6% (7 of 1163 subjects) in the naldemedine group (abdominal discomfort in 3 subjects; gastrointestinal pain in 2 subjects; gastrointestinal sounds abnormal in 1 subject; and enterocolitis in 1 subject). The enterocolitis reported by 1 subject in the naldemedine 0.2 mg group was severe in severity, but the event resolved following conservative treatment. Other events were mild or moderate in severity.

Based on the above, as there were no major differences in the incidence of gastrointestinal perforation-related events between the naldemedine 0.2 mg and placebo groups in patients with cancer or chronic non-cancer pain, naldemedine is unlikely to cause gastrointestinal perforation.

PMDA's view:
Japanese and foreign clinical studies conducted so far have shown no major differences in the incidence of gastrointestinal perforation-related events between the naldemedine 0.2 mg and placebo groups. This suggests that there are no particular problems at present. However, as cases of gastrointestinal perforation have been reported with another drug in the same class, a precaution should be included in the package insert and information should continue to be collected via post-marketing surveillance etc.

7.R.2.4.3 Major adverse cardiac events (MACE)

In the US, an increased incidence of myocardial infarction was seen in patients with chronic non-cancer pain treated with alvimopan, compared with those receiving placebo (according to the US labeling for Entereg). Alvimopan is another peripherally-acting μ-opioid receptor antagonist unapproved in Japan, and is indicated to accelerate the time to upper and lower gastrointestinal recovery following surgeries that include partial bowel resection with primary anastomosis.

The applicant's explanation on the occurrence of MACE associated with naldemedine:
The occurrence of cardiovascular death, myocardial infarction, and cerebrovascular accident (stroke) was investigated in Japanese studies in patients with cancer (Studies V9222, V9236, and V9237), Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239), and foreign studies in patients with chronic non-cancer pain (Studies V9231, V9232, and V9235). In the Japanese studies in patients with cancer (Studies V9222, V9236, and V9237) and the Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239), myocardial infarction was identified by preferred terms under “myocardial infarction (SMQ),” and cerebrovascular accident was identified by events considered by the investigator to be related to conditions associated with “central nervous system haemorrhages and cerebrovascular accidents (SMQ),” “haemorrhagic cerebrovascular conditions (SMQ),” and “ischaemic cerebrovascular conditions (SMQ).” In the foreign studies in patients with chronic non-cancer pain (Studies V9231, V9232, and V9235), the applicant collected (a) events classified under the SMQs and (b) events suspected to be MACE based on assessment of individual cases by the investigator etc. or periodic safety assessment by the sponsor; among these events, those determined to be MACE by an independent external committee, were analyzed.

In the Japanese and foreign clinical studies, cardiovascular death occurred in 0.3% (3 of 1165) of subjects in the placebo group (cardiac arrest; arteriosclerosis; and cerebrovascular accident, 1 subject each) and 0.1% (1 of 1163) of subjects in the naldemedine 0.2 mg group (myocardial infarction). A causal relationship to study drug was ruled out for all these cases.

Myocardial infarction was not reported in the naldemedine 0.2 mg group in Japanese studies in patients with cancer (Studies V9222 and V9236) or a Japanese extension study in patients with cancer (Study V9237). In the Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239), myocardial infarction occurred in 3.8% (2 of 53) of subjects treated with 0.2 mg naldemedine (blood CPK increased [2 subjects]), but their causal relationship to naldemedine was ruled out. In the foreign studies in patients with chronic non-cancer pain (up to Week 12 in Studies V9231, V9232, and V9235), the incidences of myocardial infarction were 0.3% (3 of 1165 subjects) in the placebo group (acute myocardial infarction; syncope; and angina unstable, 1 subject each) and 0.3% (3 of 1163 subjects) in the naldemedine group (acute myocardial infarction [2 subjects]; supraventricular tachycardia [1 subject]). Among these events, the following were severe in severity: syncope and angina unstable in 1 subject each in the placebo group; and acute myocardial infarction in 2 subjects and supraventricular tachycardia in 1 subject in the naldemedine 0.2 mg group. The outcomes of the events in the naldemedine 0.2 mg group (acute myocardial infarction and supraventricular tachycardia) were all reported as "resolved."

Cerebrovascular accident was not reported in the naldemedine 0.2 mg group in the Japanese studies in patients with cancer (Studies V9222 and V9236). In the Japanese extension study in patients with cancer (Study V9237), cerebrovascular accident occurred in 0.8% (1 of 131) of subjects treated with 0.2 mg naldemedine (dysarthria), but its causal relationship to naldemedine was ruled out. In the Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239), cerebrovascular accident occurred in 1.9% (1 of 53) of subjects treated with 0.2 mg naldemedine (cerebral infarction). In the foreign studies in patients with chronic non-cancer pain

(up to Week 12 in Studies V9231, V9232, and V9235), cerebrovascular accident was not reported in the placebo group, and cerebrovascular accident occurred in 0.1% (1 of 1163) of subjects in the naldemedine group (cerebrovascular accident); the event was moderate in severity.

These data show that the incidence of MACE was low in patients with cancer or chronic non-cancer pain and that there were no major differences in the incidence of MACE between the naldemedine 0.2 mg and placebo groups. Thus, naldemedine is unlikely to cause MACE.

PMDA's view:
Japanese and foreign clinical studies conducted so far have shown no major differences in the incidence of MACE between the naldemedine 0.2 mg and placebo groups. This suggests that there are no particular problems at present. However, as MACE has been reported with another drug in the same class, information should continue to be collected via post-marketing surveillance etc.

7.R.2.4.4 Opioid withdrawal syndrome and effects on opioid analgesic effects

The applicant's explanation on opioid withdrawal syndrome and effects on opioid analgesic effects:
In view of the pharmacologic effects of naldemedine, the applicant collected and analyzed events identified by preferred terms under “drug withdrawal (SMQ)” to investigate the occurrence of opioid withdrawal syndrome associated with naldemedine. Patients were defined as having “possible opioid withdrawal syndrome” if they experienced at least 3 adverse events, occurring on the same day or within 2 consecutive days, that were potentially related to opioid withdrawal syndrome.

Drug withdrawal was not reported in Japanese studies in patients with cancer (Studies V9222, V9236, and V9237). In Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239), 1 case of drug withdrawal (drug withdrawal syndrome) was reported in Study V9238, which was considered due to opioid dose reduction, and its causal relationship to naldemedine was ruled out. In foreign studies in patients with chronic non-cancer pain (up to Week 12 in Studies V9231, V9232, and V9235), the incidences of drug withdrawal were 0.6% (7 of 1165 subjects) in the placebo group and 1.0% (12 of 1163 subjects) in the naldemedine group.

One patient each in Study V9236 (diarrhoea, vomiting, pyrexia) and Study V9237 (tachycardia, arthralgia, myalgia) were identified as having possible opioid withdrawal syndrome, but all of these events resolved. In the Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239), 1 patient was identified as having possible opioid withdrawal syndrome in Study V9238 (abdominal pain, diarrhoea, vomiting); these events resolved. In the foreign studies in patients with chronic non-cancer pain (up to Week 12 in Studies V9231, V9232, and V9235), the incidences of possible opioid withdrawal syndrome were 0.5% (6 of 1165 subjects) in the placebo group and 1.6% (19 of 1163 subjects) in the naldemedine group; many of these adverse events belonged to gastrointestinal disorders. Many of the adverse events occurring in the naldemedine group belonged to gastrointestinal disorders, and can be explained by the pharmacologic effects of naldemedine. Thus, naldemedine was considered to have no central effects.

In Japanese studies in patients with cancer and Japanese studies in patients with chronic non-cancer pain, assessment of opioid withdrawal was performed using the total COWS score (Table 59). As a result, no major changes from baseline were observed in patients with cancer or chronic non-cancer pain (Table 60).

Table 59. Total COWS score

The following 11 symptoms or signs are individually rated on a 3-5 point scale and recorded.		
1. Resting pulse rate	**5. Bone or joint aches**	**9. Yawning**
2. Sweating	**6. Runny nose or tearing**	**10. Anxiety or irritability**
3. Restlessness	**7. GI upset**	**11. Gooseflesh skin**
4. Pupil size	**8. Tremor**	
Total scores used to assess overall severity of withdrawal symptoms		
5-12 = mild, 13-24 = moderate, 25-36 = moderately severe, >36 = severe		

Table 60. Change in COWS score over time (Pooled data from studies in patients with cancer [Studies V9222, V9236, and V9237] and pooled data from studies in patients with chronic non-cancer pain [Studies V9238 and V9239])

	Patients with cancer	Patients with chronic non-cancer pain
	Naldemedine 0.2 mg (N = 224)	Naldemedine 0.2 mg (N = 53)
Baseline	**0.9 ± 1.0 (224)**	**0.5 ± 0.8 (53)**
Week 2	**0.9 ± 1.1 (202)**	**0.6 ± 0.8 (51)**
Week 12	**0.9 ± 1.0 (54)**	**0.5 ± 0.8 (45)**
Week 24		**0.5 ± 0.9 (42)**
Week 36		**0.5 ± 0.8 (40)**
Week 48		**0.6 ± 0.9 (38)**
Last observation	**1.1 ± 1.5 (213)**	**0.5 ± 0.8 (50)**

Mean ± SD (n)

NRS[19)] was used to measure pain intensity to assess the effect of naldemedine on opioid analgesic effects. As a result, there were no clinically meaningful changes from baseline in naldemedine-treated patients with cancer or chronic non-cancer pain (Table 61).

Table 61. Changes in NRS score over time (Pooled data from studies in patients with cancer [Studies V9222 and V9236] and data from study in patients with chronic non-cancer pain [Study V9238])

	Patients with cancer	Patients with chronic non-cancer pain
	Naldemedine 0.2 mg (N = 155)	Naldemedine 0.2 mg (N = 43)
Baseline	**2.4 ± 1.9 (155)**	**5.4 ± 2.2 (43)**
Week 2	**2.4 ± 2.1 (136)**	**5.4 ± 2.4 (42)**
Week 12	**—**	**5.7 ± 2.2 (37)**
Week 24		**5.8 ± 2.2 (35)**
Week 36		**5.8 ± 2.3 (33)**
Week 48		**5.6 ± 2.6 (31)**
Last observation	**2.5 ± 2.2 (155)**	**5.8 ± 2.4 (40)**

Mean ± SD (n)

PMDA's view:

The results of Japanese and foreign clinical studies show that naldemedine is unlikely to cause opioid withdrawal syndrome or to impact opioid analgesic effects. However, since patients with a compromised

[19)] Intensity of cancer pain in the past 24 hours (from the time of completing patient diary entries on the previous day of assessment until the time of completing patient diary entries on the day of assessment) was measured on a 11-point scale ranging from 0 = no pain to 10 = worst possible pain (the worst pain ever) at the same time each day wherever possible.

blood-brain barrier may be at an increased risk of opioid withdrawal syndrome or reduced analgesia [see Section 6.1.2.4], a precaution should be included in the package insert and information should be collected via post-marketing surveillance etc.

7.R.3 Clinical positioning

The applicant's explanation on the clinical positioning of naldemedine in terms of choice between naldemedine and existing anti-constipating agents:

In Japan, there are no drugs approved for the treatment of OIC, and the diagnostic/treatment guidelines have not been established. Meanwhile, Guidance for proper use of medical narcotics (published by the Pharmaceutical and Food Safety Bureau, MHLW) and Guideline on drug therapy for cancer pain 2014 mention constipation as a major adverse reaction to opioid analgesics and describe how to manage it.

In Japan, osmotic laxatives (magnesium oxide, lactulose), large-bowel stimulant laxatives (sodium picosulfate, sennoside), etc. are used for the treatment of OIC in patients with cancer (Guideline on drug therapy for cancer pain 2014, Guidance for proper use of medical narcotics). Although the treatment plan for patients with chronic non-cancer pain is similar to that for patients with cancer, a chloride channel activator, lubiprostone[20)] has been approved in the US for the treatment of OIC in patients with chronic non-cancer pain.

In Japan, osmotic laxatives are often chosen as first-line agents for patients including the elderly because they are less habit-forming. However, osmotic laxatives cause adverse reactions such as abnormal electrolytes and bloating, and the risk of hypermagnesaemia in the elderly has been reported with magnesium oxide preparations. Large-bowel stimulant laxatives cause tolerance and habituation and are contraindicated in patients with spastic constipation or constipation accompanied by abdominal pain; their chronic use causes adverse reactions such as large-bowel melanosis.

Naldemedine is unlikely to interference with opioid analgesia, because it is a peripherally-acting μ-opioid receptor antagonist and does not antagonize the μ-opioid receptors in the central nervous system. Since naldemedine is effective in the treatment of OIC in both patients with cancer and patients with chronic non-cancer pain, it will offer a new treatment option for patients with OIC.

PMDA's view:

Clinical studies in patients with cancer and OIC demonstrated the efficacy of naldemedine, and clinical studies in patients with OIC and chronic non-cancer pain also showed that the efficacy of naldemedine is expected [see Section 7.R.1]. Its safety was also acceptable [see Section 7.R.2]. Thus, the usefulness of naldemedine in the treatment of OIC in patients with cancer or chronic non-cancer pain has been demonstrated. Naldemedine has a different mechanism of action from existing drugs, and can offer a new option for the treatment of OIC in patients with cancer or chronic non-cancer pain.

[20)] Approved for the treatment of chronic constipation (excluding constipation caused by organic disease) in June 2012 in Japan.

7.R.4 Indication

In Japanese clinical studies, patients with constipation symptoms listed in Table 36 were defined as having “opioid-induced constipation.” PMDA asked the applicant to explain how much healthcare professionals in clinical practice in Japan are familiar with the term opioid-induced constipation, and the intended patient population for naldemedine therapy.

The applicant's response:

The term "opioid-induced constipation" does not appear, but constipation is mentioned as a common adverse reaction to opioids in "Guideline on drug therapy for cancer pain 2014" of the Japanese Society for Palliative Medicine and "Guideline for prescribing opioid analgesics for chronic non-cancer pain" of the Japan Society of Pain Clinicians. In both patients with cancer and patients with chronic non-cancer pain, constipation occurring after the initiation of opioids, if not caused by other factors, are generally considered as “opioid-induced constipation” by healthcare professionals in Japan.

PMDA's view:

The term "opioid-induced constipation" is not used in the guidelines in Japan. However, constipation is a well-known adverse reaction to opioids, and clinical studies have demonstrated the usefulness of naldemedine in OIC patients with constipation symptoms of certain severity. Thus, there is no particular problem with the proposed indication of OIC.

A final conclusion on the indication for naldemedine will be made, taking account of comments from the Expert Discussion.

7.R.5 Dosage and administration

The applicant's explanation on the rationale for dose selection for a Japanese phase III study in patients with cancer (Study V9236) and Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239):

A multi-regional (Japan and Korea) phase II study in patients with cancer (Study V9222) showed statistically significant differences in the primary endpoint “the change from baseline in weekly frequency of SBMs during the 2-week treatment period” between the naldemedine 0.1, 0.2, or 0.4 mg and placebo groups (Table 37). On the other hand, no statistically significant difference was observed in the secondary endpoint “the SBM responder rate during the 2-week treatment period” between the naldemedine 0.2 and 0.4 mg groups, and the incidence of diarrhoea tended to be higher in the naldemedine 0.4 mg group than in the naldemedine 0.2 mg group (44.8% in the naldemedine 0.2 mg group, 57.1% in the naldemedine 0.4 mg group). Thus, the 0.2 mg dose was selected for a Japanese phase III study in patients with cancer (Study V9236).

Since the Japanese phase III study in patients with cancer (Study V9236) demonstrated the superiority of naldemedine 0.2 mg over placebo and its acceptable safety, the 0.2 mg dose was considered appropriate for patients with cancer.

The pharmacologic effects of naldemedine and the mechanism of development of OIC suggest that the effective dose of naldemedine for OIC is the same for both patients with chronic non-cancer pain and those with cancer. A foreign phase II study in patients with chronic non-cancer pain (Study V9221) showed significant differences in the primary endpoint "the change from baseline in weekly frequency of SBMs during the last 2 weeks of the 4-week treatment period" between the naldemedine 0.2 or 0.4 mg and placebo groups. On the other hand, there was no significant difference between the naldemedine 0.1 mg and placebo groups, and the incidences of diarrhoea and abdominal pain tended to be higher in the naldemedine 0.4 mg group than in the naldemedine 0.2 mg group (diarrhoea, 5.0% in the naldemedine 0.2 mg group, 18.0% in the naldemedine 0.4 mg group; abdominal pain, 8.3% in the naldemedine 0.2 mg group, 14.8% in the naldemedine 0.4 mg group). Hence, the optimal dose of naldemedine was determined to be 0.2 mg for patients with chronic non-cancer pain outside Japan. The 0.2 mg dose was therefore selected for Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239). The Japanese long-term treatment studies in patients with chronic non-cancer pain (Studies V9238 and V9239) showed improvement in the PAC-SYM responder rate (Table 52) etc. over a long period of time and acceptable safety. Thus, the applicant considers that there is no particular problem with the proposed 0.2 mg dose of naldemedine for patients with chronic non-cancer pain.

The applicant's explanation on naldemedine dose reduction and interruption:
If subjects were suspected to have decreased QOL due to adverse events of naldemedine, etc., naldemedine interruption and dose reduction to 0.1 mg were permitted from the beginning of a Japanese extension study in patients with cancer (Study V9237) and at Week 3 and thereafter in Japanese studies in patients with chronic non-cancer pain (Studies V9238 and V9239). However, only 5 of 184 patients (2.7%) in these 3 studies received 0.1 mg of naldemedine, of whom 3 patients later had their dose increased to 0.2 mg. Naldemedine was interrupted in 10.9% (20 of 184) of the patients. Of the 20 patients, 12 resumed naldemedine at 0.2 mg, 4 resumed naldemedine at 0.1 mg, and 4 discontinued naldemedine. Of the 12 patients who resumed naldemedine at 0.2 mg, 8 remained on 0.2 mg naldemedine until the end of the study. Of the 4 patients who resumed naldemedine at 0.1 mg, 2 had their dose increased to 0.2 mg and remained on 0.2 mg until the end of the study, 1 patient interrupted treatment again and then discontinued treatment, and only 1 patient remained on 0.1 mg naldemedine until the end of the study. Based on the above, both patients with cancer and patients with chronic non-cancer pain can continue treatment without dose reduction to 0.1 mg if they interrupt treatment as appropriate. Thus, dose reduction to 0.1 mg was considered unnecessary.

PMDA's view:
There is no particular problem with the proposed 0.2 mg dose of naldemedine for patients with cancer or chronic non-cancer pain based on Japanese studies.

Dose reduction is not recommended by the proposed dosage and administration; this is acceptable at present for the following reasons: (a) only a limited number of patients had their dose reduced to 0.1 mg in Japanese clinical studies; (b) 0.2 mg naldemedine was administered for ≤14 weeks to patients with cancer and for ≤48 weeks to patients with chronic non-cancer pain; these patients received treatment with no major problems because they were allowed to interrupt treatment as needed.

Administration of naldemedine without regard to meals is justified, because Japanese and foreign clinical studies evaluating food effect showed that food had no significant effects on the pharmacokinetics of naldemedine [see Section 6.R.1].

A final conclusion on dosage and administration for naldemedine will be made, taking account of comments from the Expert Discussion.

7.R.6 Concomitant medications

Naldemedine is expected to be used with existing laxatives in the treatment of OIC in patients with cancer or chronic non-cancer pain. PMDA asked the applicant to explain the efficacy and safety of naldemedine with concomitant laxative use.

The applicant's response:

In Japanese phase II and III studies in patients with cancer (Studies V9222 and V9236), 83.9% (130 of 155) of patients in the naldemedine 0.2 mg group remained on a laxative regimen during the study period. The SBM responder rates during the 2-week treatment period in the naldemedine 0.2 mg group with and without laxative use were 73.8% (96 of 130 subjects) and 72.0% (18 of 25 subjects), respectively, showing no effects of concomitant laxative use. The incidences of adverse events in the naldemedine 0.2 mg group with and without laxative use were 67.7% (88 of 130 subjects) and 60.0% (15 of 25 subjects), respectively, showing no clinical problems with concomitant laxative use. In long-term treatment studies in patients with chronic non-cancer pain (Studies V9238 and V9239), 90.6% (48 of 53) of patients remained on a laxative regimen during the study period. The SBM responder rates during the 2-week treatment period with and without laxative use were 80.9% (38 of 47 subjects) and 100% (5 of 5 subjects), respectively, and the incidences of adverse events were 89.6% (43 of 48 subjects) and 80.0% (4 of 5 subjects), respectively. Although the number of patients without concomitant laxative use was limited, there were no major problems.

PMDA confirmed that at present, there are no particular problems with the efficacy and safety of naldemedine with concomitant laxative use. However, Japanese studies limited the types of concomitant laxatives that subjects can use, and a wide variety of laxatives are expected to be used concomitantly with naldemedine for the treatment of OIC in clinical practice. Thus, it is necessary to continue to collect information on the safety and efficacy of naldemedine with concomitant laxative use, etc. via post-marketing surveillance etc.

7.R.7 Post-marketing investigations

The applicant plans to conduct a post-marketing use-results survey in patients with cancer and a post-marketing specified use-results survey of long-term treatment in patients with chronic non-cancer pain (Table 62 and Table 63).

Table 62. Outline of use-results survey in patients with cancer (draft)

Objective	**To ascertain the safety and efficacy of naldemedine in patients with cancer in routine clinical settings and identify unknown adverse drug reactions, factors affecting safety or efficacy, factors contributing to the occurrence of gastrointestinal symptoms or serious gastrointestinal symptoms, etc.**
Survey method	**Central registry system**
Population	**Patients with cancer and OIC**
Target sample size	**1200 patients**
Survey period	**2 years and 6 months (enrollment period, 2 years and 3 months)**
Observation period	**12 weeks**
Main survey items	**· Patient characteristics (age, gender, concurrent diseases, medical history, details of malignant tumors [primary site, presence or absence of metastasis, PS], etc.)** **· Use of naldemedine (dose, route of administration, duration of treatment, reason for treatment discontinuation, etc.)** **· Use of opioids (name of drug, route of administration, daily dose, duration of treatment, etc.)** **· Use of laxatives (name of drug, route of administration, daily dose, duration of treatment, etc.)** **· Use of concomitant medications (excluding opioids and laxatives) (concomitant use [YES/NO], name of concomitant medication, daily dose, duration of treatment, etc.)** **· Efficacy (improvement in frequency of bowel movements, improvement in bowel symptoms [hardness of stools, straining, feeling of incomplete evacuation])** **· Adverse events (onset date, seriousness, action taken, outcome, a causal relationship to naldemedine, etc.)**

Table 63. Outline of specified use-results survey of long-term treatment in patients with chronic non-cancer pain (draft)

Objective	**To ascertain the safety and efficacy of naldemedine in patients with chronic non-cancer pain in routine clinical settings (including long-term use) and identify unknown adverse drug reactions, factors affecting safety or efficacy, etc.**
Survey method	**Central registry system**
Population	**Patients with OIC and chronic non-cancer pain**
Target sample size	**350 patients**
Survey period	**5 years and 2 months (enrollment period, 4 years and 2 months)**
Observation period	**52 weeks**
Main survey items	**· Patient characteristics (age, gender, concurrent diseases, medical history, cause of chronic pain, etc.)** **· Use of naldemedine (dose, route of administration, duration of treatment, reason for treatment discontinuation, etc.)** **· Use of opioids (name of drug, route of administration, daily dose, duration of treatment, etc.)** **· Use of laxatives (name of drug, route of administration, daily dose, duration of treatment, etc.)** **· Use of concomitant medications (excluding opioids and laxatives) (concomitant use [YES/NO], name of concomitant medication, daily dose, duration of treatment, etc.)** **· Efficacy (improvement in frequency of bowel movements, improvement in bowel symptoms [hardness of stools, straining, feeling of incomplete evacuation])** **· Adverse events (onset date, seriousness, action taken, outcome, a causal relationship to naldemedine, etc.)**

PMDA considers that post-marketing surveillance should also cover the following issues. The details of post-marketing surveillance will be finalized, taking account of comments from the Expert Discussion.

● Long-term safety and efficacy of naldemedine in patients with cancer or chronic non-cancer pain

● Safety and efficacy of naldemedine with concomitant laxative use, etc.

● Diarrhoea, gastrointestinal perforation, cardiovascular events, opioid withdrawal syndrome, and effects on opioid analgesic effects

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and

Cosmetics. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-01, CTD 5.3.5.1-02, CTD 5.3.5.2-01, CTD 5.3.5.2-02, CTD 5.3.5.2-03) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The results showed that the clinical studies as a whole were conducted in compliance with GCP. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted. Although the outcome of the overall assessment of the studies was not affected significantly, the inspection revealed the following findings at a study site used by the applicant, and the head of the relevant medical institution was notified of these findings requiring improvement.

Findings requiring improvement

Study site

● Protocol deviations (non-compliance with the rules for reporting serious adverse events, non-compliance with the rules for subject withdrawal)

9. Overall Evaluation during Preparation of the Review Report (1)

PMDA has concluded that the data submitted demonstrate the efficacy of naldemedine in the treatment of opioid-induced constipation and acceptable safety in view of the benefits indicated by the data submitted. Naldemedine is clinically meaningful because it offers a new treatment option for patients with opioid-induced constipation. PMDA considers that the efficacy, safety, indication, dosage and administration, and post-marketing investigations of naldemedine need further discussion.

PMDA has concluded that naldemedine may be approved if naldemedine is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

January 13, 2017

Product Submitted for Approval

Brand Name	Symproic Tablets 0.2 mg
Non-proprietary Name	Naldemedine Tosilate
Applicant	Shionogi & Co., Ltd.
Date of Application	March 30, 2016

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy, safety, indication, and dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusions presented in "6.R.3 Drug interactions," "7.R.1 Efficacy," "7.R.2 Safety," "7.R.4 Indication," and "7.R.5 Dosage and administration" in the Review Report (1). The expert advisors made the following comments:

- Healthcare professionals and patients should be advised to discontinue naldemedine if opioid therapy is also discontinued, because naldemedine is a peripherally acting opioid antagonist and exerts its effects against OIC.
- Post-marketing information should be collected to determine whether there is a medical need for a lower-strength tablet, and its development should be initiated as needed.

Based on the comments from the Expert Discussion, PMDA instructed the applicant to modify the wording (of the original Japanese text) for Indication as shown below (this does not affect the English translation), and to use the following wording for Dosage and Administration and Precautions for Dosage and Administration. The applicant responded appropriately, and PMDA accepted it. The applicant explained that post-marketing information will be collected to determine whether there is a medical need for a lower-strength tablet and its development will be considered, and PMDA accepted it.

Indication

Opioid-induced constipation

Dosage and Administration

The usual adult dosage is 0.2 mg of naldemedine administered orally once daily.

Precautions for Dosage and Administration

Discontinue naldemedine if opioid therapy is also discontinued.

1.2 Risk management plan (draft)

The expert advisors made the following comment and supported PMDA's conclusion presented in "7.R.7 Post-marketing investigations" in the Review Report (1).

- Information should continue to be collected via post-marketing surveillance to investigate opioid withdrawal syndrome and reduced opioid analgesia.

In view of the discussion above, PMDA requested that the risk management plan (draft) for naldemedine include the safety and efficacy specifications presented in Table 64, and that the applicant conduct additional pharmacovigilance activities and risk minimization activities presented in Table 65, a use-results survey presented in Table 66, and a specified use-results survey presented in Table 67. The applicant responded appropriately, and PMDA accepted it.

Table 64. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	**Important potential risks**	**Important missing information**
· Diarrhoea	**· Opioid withdrawal syndrome** **· Reduced opioid analgesia** **· Gastrointestinal perforation** **· Cardiovascular events**	**· None**
Efficacy specification		
· Efficacy in routine clinical settings		

Table 65. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	**Additional risk minimization activities**
· Early post-marketing phase vigilance **· Use-results survey (survey in patients with cancer)** **· Specified use-results survey (survey of long-term treatment in patients with chronic non-cancer pain)**	**· Disseminate information gathered during early post-marketing phase vigilance.**

Table 66. Outline of use-results survey in patients with cancer (draft)

Objective	**To ascertain the safety and efficacy of naldemedine in patients with cancer in routine clinical settings and identify unknown adverse drug reactions, factors affecting safety or efficacy, etc.**
Survey method	**Central registry system**
Population	**Patients with cancer and OIC**
Target sample size	**1200 patients**
Survey period	**2 years and 6 months (enrollment period, 2 years and 3 months)**
Observation period	**12 weeks**
Main survey items	**· Patient characteristics (age, gender, concurrent diseases, medical history, details of malignant tumors [primary site, presence or absence of metastasis, PS], etc.)** **· Use of naldemedine (dose, route of administration, duration of treatment, reason for treatment discontinuation, etc.)** **· Use of opioids (name of drug, route of administration, daily dose, duration of treatment, etc.)** **· Presence or absence of opioid withdrawal symptoms, presence or absence of reduced opioid analgesia** **· Use of laxatives (name of drug, route of administration, daily dose, duration of treatment, etc.)** **· Use of concomitant medications (excluding opioids and laxatives) (concomitant use [YES/NO], name of concomitant medication, daily dose, duration of treatment, etc.)** **· Efficacy (improvement in frequency of bowel movements, improvement in bowel symptoms [hardness of stools, straining, feeling of incomplete evacuation])** **· Adverse events (onset date, seriousness, action taken, outcome, a causal relationship to naldemedine, etc.)**

Table 67. Outline of specified use-results survey of long-term treatment in patients with chronic non-cancer pain (draft)

Objective	**To ascertain the safety and efficacy of naldemedine in patients with chronic non-cancer pain in routine clinical settings (including long-term use) and identify unknown adverse drug reactions, factors affecting safety or efficacy, etc.**
Survey method	**Central registry system**
Population	**Patients with OIC and chronic non-cancer pain**
Target sample size	**350 patients**
Survey period	**5 years and 2 months (enrollment period, 4 years and 2 months)**
Observation period	**52 weeks**
Main survey items	**· Patient characteristics (age, gender, concurrent diseases, medical history, cause of chronic pain, etc.)** **· Use of naldemedine (dose, route of administration, duration of treatment, reason for treatment discontinuation, etc.)** **· Use of opioids (name of drug, route of administration, daily dose, duration of treatment, etc.)** **· Presence or absence of opioid withdrawal symptoms, presence or absence of reduced opioid analgesia** **· Use of laxatives (name of drug, route of administration, daily dose, duration of treatment, etc.)** **· Use of concomitant medications (excluding opioids and laxatives) (concomitant use [YES/NO], name of concomitant medication, daily dose, duration of treatment, etc.)** **· Efficacy (improvement in frequency of bowel movements, improvement in bowel symptoms [hardness of stools, straining, feeling of incomplete evacuation])** **· Adverse events (onset date, seriousness, action taken, outcome, a causal relationship to naldemedine, etc.)**

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

Opioid-induced constipation

Dosage and Administration

The usual adult dosage is 0.2 mg of naldemedine administered orally once daily.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.