13 December 2018
EMA/466/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rizmoic

International non-proprietary name: naldemedine

Procedure No. EMEA/H/C/004256/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase (SGPT)
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
APD_{30-90}	difference between the action potential duration at 30% and 90%
AST	aspartate aminotransferase (SGOT)
AUC	area under the concentration-time curve
AUC_{0-24hr}	area under the concentration-time curve from time 0 to 24 hours
AUC_{0-inf}	area under the concentration-time curve from time 0 to infinity
$AUC_{0-\tau}$	area under the concentration-time curve from time 0 to the time of the last measureable concentration
BA	bioavailability
BBB	blood-brain barrier
BCRP	breast cancer resistance protein
BCS	biopharmaceutical classification system
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BF	Bowel Function
BFI	Bowel Function Index
BM	bowel movement
BMCA	Bowel movement and constipation assessment
BMI	body mass index
BSEP	bile salt export pump
BSS	Bristol Stool Scale
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL_{cr}	creatinine clearance
CLtot	total clearance
C_{max}	maximum plasma concentration
CMA	Critical Material Attribute

CNS	central nervous system
COWS	Clinical Opiate Withdrawal Scale
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CSBM	complete spontaneous bowel movement
CV	coefficient of variation
CYP	cytochrome P450
DCF	Data Correction Form
DoE	Design of Experiments
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
eDiary	electronic diary
ED50 (80)	50% (80%) effective dose
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ESRD	end-stage renal disease
EU	European Union
FAMHP	Federal Agency for Medicines and Health Products
FAS	full analysis set
FDA	Food and Drug Administration
FMEA	Failure Modes and Effects Analysis
FOB	Functional observational battery
G	Glucuronide
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
GMR	geometric mean ratio
hERG	human Ether-à-go-go-Related Gene
HAS	human serum albumin
IC_{50}	concentration producing half maximal effect
ICH	International Conference on Harmonisation
ITT	Intent-to-Treat
K_b	binding constant

Ki	inhibition constant
Kobs	association rate constant
Koff	dissociation rate constant
LIR	inadequate response to laxatives
LLOQ	lower limit of quantification
LS	least-squares
MAA	Marketing Authorisation Application
MATE	multidrug and toxin extrusions
MDRD	modification of diet in renal disease
MED	morphine-equivalent dose
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MHRD	Maximum human relevant dose
mITT	modified Intent-to-Treat
MMRM	mixed-effect model repeated measures
MNTX	methylnaltrexone
Naldemedine 3-G	naldemedine 3-o-β-D-glucuronide
Naldemedine 6-G	naldemedine 6-O-β-D-glucuronide
NDA	New Drug Application
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NRS	Numeric Rating Scale
OAT	organic anion transporter
OATP	organic anion transporting peptide
OBD	opioid-induced bowel dysfunction
OCT	organic cation transporter
OIC	opioid-induced constipation
PAC-QOL	Patient Assessment of Constipation Quality of Life Questionnaire
PAC-SYM	Patient Assessment of Constipation Symptoms Questionnaire
PAMORA	peripherally-acting μ-opioid receptor antagonist
PDCO	Paediatric Committee

PGIC	Global Impression of Change
P-gp	P-glycoprotein
PIP	Paediatric Investigation Plan
PK	pharmacokinetic/pharmacokinetics
PK/PD	pharmacokinetics/pharmacodynamics
POC	proof of concept
PRN	pro re nata (as required)
PT	preferred term
QOL	Quality of Life
QTTP	Quality Target Product Profile
QWBA	Quantitative whole-body autoradiography
RMP	Risk Management Plan
SADR	serious adverse drug reaction
SAE	serious treatment-emergent adverse event
SBM	spontaneous bowel movement
SD	standard deviation
SF	Short Form
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
SOC	System Organ Class
T½	Time until the binding of [3H]-ligand to human or rat μ-opioid receptor decreases to 50% after the addition of excess amount of unlabeled ligand
$T_{½,z}$	Terminal elimination half-life
T.BIL	Total bilirubin
TDD	total daily dose
TEAE	treatment-emergent adverse event
T_{max}	time to maximum plasma concentration
UGT	uridine diphosphate glucuronosyltransferase
UK	United Kingdom
US	United States
Vdss	Volume of distribution at steady state
Vz/F	apparent volume of distribution based in the terminal phase

WHO	World Health Organization

Not all abbreviations may be used

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Shionogi Limited submitted on 1 March 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Rizmoic, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. During the evaluation the applicant for the above medicinal product was transferred to Shionogi B.V.

The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 June 2015.

The applicant applied for the following indication: treatment of opioid-induced constipation (OIC) in adult patients.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that naldemedine was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0044/2017 the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0044/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance naldemedine contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Mark Ainsworth Co-Rapporteur: Bart Van der Schueren

The application was received by the EMA on	1 March 2017
The procedure started on	23 March 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	12 June 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	12 June 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	23 June 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 July 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 December 2017
The following GCP and GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
• GCP inspections at two investigator sites located in the United States and the sponsor site in the United States were conducted between 10 July 2018 and 1 September 2018. The outcome of the inspection carried out was issued on	29 September 2017
• GMP inspection of the site Charles River Laboratories Contract Manufacturing PA, LLC, Three Chelsea Parkway Suite 305 Boothwyn Pennsylvania 19061 United States was carried out on 14-16 February 2017. The outcome of the inspection carried out was issued on	21 June 2017
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	29 January 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 February 2018
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	22 February 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 March 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 April 2018
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP agreed on a 2nd list of outstanding issues to be sent to the applicant on	26 April 2018
The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on	12 November 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the	28 November 2018

List of Outstanding Issues to all CHMP members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Rizmoic on	13 December 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Opioid analgesics have been used extensively for the treatment of moderate to severe pain both in non-cancer and cancer pain. However, opioid use is associated with a number of adverse events (AEs), with the most common occurring in the gastrointestinal system such as constipation, nausea, vomiting, abdominal cramping, bloating and abdominal pain. Opioid-induced constipation (OIC) is the most common adverse drug reaction (ADR) occurring with the chronic use of opioids.

The signs and symptoms of OIC can significantly interfere with activities of daily living thereby adversely affecting the quality of life (QOL) of the patient, and may be even more distressing for the patient than the pain of the condition itself.

2.1.2. Epidemiology

In patients with chronic non-cancer pain receiving opioid therapy, OIC is the most commonly reported and undesirable side effect. A systematic literature review revealed that approximately 40% to 50% of patients with chronic non-cancer pain receiving chronic opioids for pain experienced OIC.

The prevalence of OIC in patients with cancer is very high, ranging from approximately 70% to 85% of patients with cancer taking opioids. There is no (or extremely slow) development of tolerance to the constipating effects of opioid therapy, particularly with codeine, dihydrocodeine, morphine, fentanyl, oxycodone, and hydromorphone.

Unrelieved constipation symptoms may add to the burden of pain and underlying illness, and may dissuade patients from using the required analgesic dose to achieve effective pain. The longer-term consequences of constipation can result in substantial morbidity (eg, rectal pain, bowel obstruction, rupture) and, in rare cases, death.

2.1.3. Aetiology and pathogenesis

Opioid receptors are widely distributed in the human body. The principal effect of opioids in the gastrointestinal tract is inhibition of gut motility as a result of μ-opioid receptor stimulation in the intestinal submucosa. This leads to delayed gastric emptying, increased pyloric sphincter tone, and prolonged intestinal transit. The resultant decrease in intestinal motility prolongs contact between the gut contents and the intestinal mucosa, resulting in increased fluid absorption. In addition, stimulation of mucosal μ-opioid receptors activates a reflex arc that leads to further fluid resorption and reduced intestinal secretions. Together, these effects result in the formation of dry, hard stools that are difficult to pass.

2.1.4. Clinical presentation, diagnosis

As mentioned above, OIC is a major side effect of chronic opioid use and persists unless properly treated. A high number of chronic opioid users are confronted with OIC, which can have a serious impact on daily activities and ability to work. If not managed properly, there is a risk for inadequate pain management since patients will lower opioid dosage when confronted with high impact, persistent OIC.

2.1.5. Management

There are a range of medicinal products and approaches currently available for the treatment of OIC. However, many standard laxatives are not effective in treating the constipation caused by opioids. Laxatives are the most common treatment for OIC and include gastrointestinal stimulants, anionic surfactants, osmotic laxatives, and bulk-forming laxatives. Stimulant laxatives act on the intestinal mucosa, increasing water and electrolyte secretion, and stimulating peristaltic action. Anionic surfactants cause changes in absorptive cell membranes, which result in intestinal secretion. Osmotic laxatives draw water to the colon, hydrating the stools. Bulk-forming laxatives increase stool frequency, water content and faecal solids.

Currently available peripherally-acting μ-opioid receptor antagonist (PAMORAs) include methylnaltrexone bromide (Relistor) and naloxegol (Moventig) which have been approved in the EU. At present, none of the above mentioned products are approved for first line treatment of OIC in the EU.

The WHO guideline for cancer pain relief recommends using prophylactic laxative as the first-line preventative treatment for OIC, initiated at the same time as opioid treatment (WHO, 1996). Strategies for subsequent lines of treatment should prophylactic measures fail, vary considerably from no recommendations to various pharmacological suggestions (eg, increasing laxative dose, combining laxatives, opioid rotation, and manual disimpaction). Patients need to cycle through multiple OIC regimens to find one that is effective, and a substantial portion of patients with OIC cannot obtain adequate control with laxatives.

About the product

Rizmoic (naldemedine) is formulated as a 0.2 mg film-coated tablet to be administered once daily with or without food. Naldemedine acts as an antagonist at the μ-, δ-, and κ-opioid receptors, and has no agonistic activity at any of these opioid receptors. Naldemedine functions as a μ-opioid receptor antagonist in peripheral tissues, in particular the enteric nervous system in the gastrointestinal tract, thereby decreasing the constipating effects of opioids without reversing centrally-mediated opioid effects.

Naldemedine is a derivative of naltrexone to which a side chain has been added that increases the molecular weight and the polar surface area, thereby reducing its ability to cross the blood brain barrier (BBB); the CNS penetration of naldemedine is expected to be negligible at the recommended dose. Additionally, naldemedine is a substrate of the P-glycoprotein (P-gp) efflux transporter, which may also be involved in reducing naldemedine penetration into the CNS. Based on this, naldemedine is expected to exert anti-constipating effects on opioids without reversing their centrally-mediated analgesic effects.

This is a MAA according to optional scope of Article 3(2)(a) of regulation (EC)726/2004 – as a new active substance.

The proposed indication at submission was: Rizmoic is indicated for the treatment of opioid-induced constipation (OIC) in adult patients.e

As strictly laxative naïve patients have not been studied the indication was amended during this procedure to bring it in line with the studied patient population as follows:

The approved indication is: Rizmoic is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have previously been treated with a laxative.

The approved posology is 200 micrograms (one tablet) once daily. Rizmoic may be used with or without laxative(s).

Type of Application and aspects on development

During the design and initiation of the Phase 3 programme for Rizmoic (naldemedine), there were no established EU regulatory guidelines for chronic constipation. In February of 2014, the draft EU Guideline on the Evaluation of Medicinal Products for the Treatment of Chronic Constipation was published (EMA/CHMP/336243, draft version dated 20 February 2014 and finalised in June 2015). No EMA scientific advice has been given during the development of Rizmoic (naldemedine).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing naldemedine tosylate, equivalent to 200 micrograms of naldemedine free base, as active substance.

Other ingredients are:

Tablet core: mannitol, croscarmellose sodium, magnesium stearate

Film coating : hypromellose, talc, yellow iron oxide (E172)

The product is available in aluminium/aluminium blister as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of naldemedine tosylate is 17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,6,14-trihydroxy-*N*-[2-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]morphinan-7-carboxamide 4-methylbenzenesulfonic acid corresponding to the molecular formula $C_{32}H_{34}N_4O_6 \cdot C_7H_8O_3S$. It has a relative molecular mass of 742.84 g/mol and the following structure:

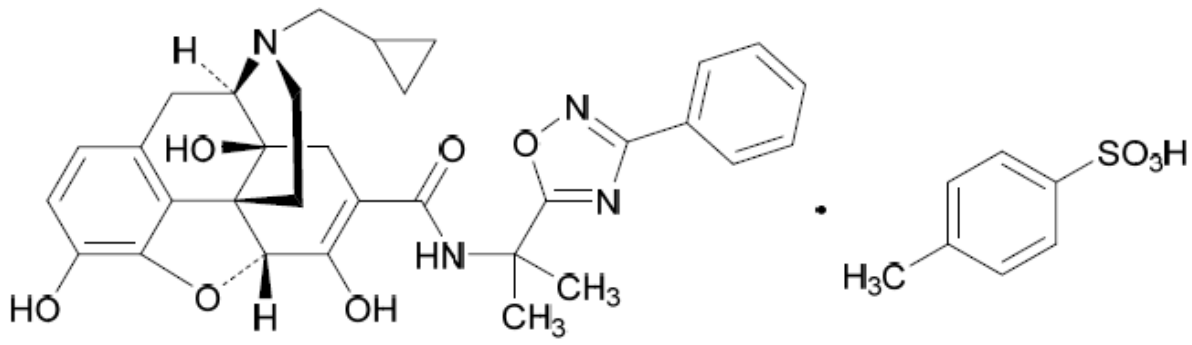


Figure 1 Active substance structure

Its chemical structure was elucidated by a combination of elemental analysis, mass spectrometry, UV, IR and ^{1}H & ^{13}C NMR spectroscopy. The structure is also supported by the synthetic route. The molecule contains four chiral centres. Only one specific enantiomer is manufactured. Enantiomeric purity is adequately controlled.

Naldemedine tosylate is a white to light tan non-hygroscopic powder. Its solubility is high over the physiological pH range and it is classified as class 3 according to the Biopharmaceutic Classification System (BCS).

Naldemedine tosylate exhibits polymorphism and results of investigations showed that the desired polymorphic form, is consistently produced under the conditions selected and registered in the commercial manufacturing process.

Other identified solid state forms are pseudo polymorphs and solvates. In addition, solvates can form in different solvents. However, these solvents are not used in the manufacturing process. All batches including DoE have consistently generated the selected form proposed for marketing. Crystalline form does not change during stability studies (see stability section).

Manufacture, characterisation and process controls

Naldemedine tosylate is synthesized in three main steps using commercially available well defined starting materials with acceptable specifications,

The process intended for commercial production uses the same synthetic route which was used to prepare the active substance used in phase 3 clinical trials, late non-clinical studies and stability studies.

To note, in its original submission the applicant proposed a starting material which was not acceptable since the proposed GMP manufacturing process involved multiple chemical transformation steps in a telescoped sequence without isolation of intermediates. That compound was a custom-synthesised chemical. The synthesis, supplier and purity profile of its precursors were not disclosed and therefore changes affecting the purity profile were not under GMP control. In addition, potential mutagenic impurities formed upstream and the chemical steps, where these impurities are formed, are critical and therefore should be part of the registered synthetic route. The major objection asking the applicant to redefine the starting material further back in the synthesis and update all relevant sections of the dossier was adequately addressed and resulted in the synthesis described in the dossier.

The development of the manufacturing process of naldemedine tosyate is based on an enhanced Quality by Design (QbD) approach. Prior knowledge, risk assessments, multivariate experiments and scientific knowledge were used to identify and understand process parameters and process steps that impact CQAs and to develop a control strategy including proven acceptable ranges (PARs) for input materials and operating conditions for commercial use. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

The active substance CQAs are: impurities potentially present in the active substance based on ICH Q3A, genotoxic impurities based on ICH M7, residual solvents based on ICH Q3C, description, assay, p-toluene sulfonic acid, optical rotation, water content, residue on ignition, crystalline form, particle size and metals based on ICH Q3D.

A mutagenic assessment of the synthetic route has been conducted in order to ensure that exposure to mutagenic impurities was limited to the threshold of toxicological concern (TTC) of not more than 1.5 µg/day for an individual mutagenic impurity and not more than 5 µg/day for total mutagenic impurities in accordance with ICH M7 for a drug for long term use. Mutagenic impurities are controlled by specifications for the relevant materials or by control of the manufacturing process.

A risk assessment to identify the potentially critical manufacturing process parameters (pCPPs) against the active substance CQAs in the manufacturing process of naldemedine tosilate was conducted. This was followed by a screening 2-level fractional factorial design of experiments (DoE) study conducted at each step to investigate the impact of process parameter variability on the CQA and define acceptable ranges.

A process verification study was conducted at pilot scale in order to confirm that the conclusions made on process performance and the overall control strategy of the active substance CQA derived from laboratory

experiments are valid during manufacture at commercial scale. In addition, results of process validation at commercial scale were provided. All results met the specification.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Two processes, named route A and route B were employed during naldemedine tosylate manufacturing process development. These two routes mainly differ in the use of starting materials. The commercial process consists of minor modifications and/or optimizations made to route B1 due to change in manufacturing site. To date, nine batches of naldemedine tosylate have been completed among three batches produced following the commercial process (route B2) at the proposed production site. The purity of the active substance has improved over the course of development and the proposed commercial process, route B2, yields active substance of consistent quality.

The active substance is packaged in double low-density polyethylene bags and sealed with plastic ties. The bags are stored in a secondary container for shipping within a metal, fibre or plastic container. The low-density polyethylene complies with the requirements of Ph. Eur. 3.1.3 the 9th edition “Polyolefins” except for “Supplementary Test” and the relevant requirements of Regulation (EU) No.10/2011, on plastic materials and articles intended to come into contact with food, as amended.

Specification

The active substance specification includes tests for description, identification (UV, IR), related substances (HPLC), residual solvents (GC), water content (KF), residue on ignition (Ph. Eur.), assay (HPLC) and particle size (laser diffraction).

The active substance specification includes relevant test parameters according to the requirements of ICH Q6A and the applied limits have been acceptably justified using analysis of representative batches of naldemedine tosylate and relevant ICH guidelines.

Actual and potential genotoxic impurities formed during the manufacture of naldemedine tosylate have been discussed and their control justified. A maximum recommended exposure of 0.57% for each potential mutagen is based upon the Threshold of Toxicological Concern of 1.5 µg/day with respect to a naldemedine tosylate daily dose of 0.26 mg for long term use (>10 years) in accordance with ICH M7.

The contents of the three tosylate impurities are determined by the related substances method. These three impurities are not specified but controlled by the active substance specification at not more than 0.10% as unspecified impurities. Other impurities are controlled in the relevant intermediate(s).The limit for total impurities was tightened during the evaluation as requested. A discussion of parameters proposed to be excluded from testing has been presented.

The fate of all solvents present in the starting materials or used in the manufacturing process has been assessed. A GC method has been developed for detection of residual solvents in naldemedine tosylate. The proposed specification limits are in line with ICH Q3C.Particle size of the active substance has an impact on appearance of the coated tablets. Therefore, a milling step is performed in the commercial process and a specification for active substance particle size has been defined.

A justification for the omission of tests for optical rotation, crystalline form, microbial limits, elemental impurities and benzene has been provided.

The omission of a test for optical rotation has been justified

As indicated above, crystalline form investigations confirmed that there is a single crystalline form of naldemedine tosylate. All purified, three representative batches of non-milled naldemedine tosylate, and active substance from milling studies and routine batches have been confirmed to be the selected form by XRPD, indicating that the milling process does not affect the crystalline form of naldemedine tosylate.

Microbiological limit test was performed on the primary stability batches of naldemedine tosylate. No growth was observed under the long-term (30 °C / 65 % RH) conditions after 60 months storage. Additionally, the water content of naldemedine tosylate under the long-term conditions at initial and after 60 months storage was low Therefore, the microbiological risk for the active substance is considered to be low and no specification is proposed in naldemedine tosylate for the microbial limit test.

The risk assessment identified potential elemental impurities for naldemedine tosylate. These elemental impurities are already controlled by the specification for residue on ignition.

Benzene is a potential impurity in other solvents which are used in the manufacturing process of naldemedine tosylate. Benzene was not detected in seven representative batches. The data demonstrated that it was purged to a level of not detected which demonstrates the efficacy with which benzene is purged. These data support the proposal not to test commercial batches of naldemedine tosylate for benzene.

The in-house developed analytical procedures have been acceptably described and adequately validated in accordance with ICH Q2 (R1) requirements. Satisfactory information regarding the reference standards used for assay testing has been presented.

A comprehensive amount of batch analysis data are presented from different development campaigns. Specifically, batch analysis data from three commercial scale batches of the active substance manufactured with the proposed commercial route and three additional batches from previous development routes have been provided. The results are within the specifications in force at the time and are consistent from batch to batch.

Naldemedine is packaged in double low-density polyethylene (LDPE) food grade plastic bags which are placed in a secondary container. Information on the packaging is sufficient and includes adequate declaration for compliance with EU Regulation.

Stability

Stability data from three pilot scale batches of active substance manufactured at the development site and stored in a container closure system representative of that intended for the market for up to 60 months under long term conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Data from 3 production scale batches manufactured at the proposed commercial site stored at long term condition (30°C/65% RH) for 18 months and at accelerated condition (40°C/75% RH) for 6 months in the intended commercial packaging were also submitted. At both sites the batches were manufactured according to the proposed commercial process.

The following parameters were tested: description (appearance), identification (IR), optical rotation, related substances, water content, assay, crystalline form, particle size distribution, and microbial limits (TAMC/TYMC).

No degradation was seen in any of the parameters tested at any of the storage conditions. A slight increase was observed in water content. However, all results complied with the specification. The results

demonstrate that the stability of naldemedine tosylate manufactured at the commercial site is comparable to that from the pilot scale batches.

Photostability testing following the ICH guideline Q1B was performed on one batch. This study confirmed that naldemedine in solid state is not sensitive to light.

Results on stress conditions (high temperature, high temperature and high humidity, high humidity) were also provided on one batch. The results demonstrate the chemical and physical stability of naldemedine tosylate at all storage conditions. No significant changes were observed in description (appearance), identification (IR), optical rotation, related substances, water, assay, crystalline form and particle size distribution, and all results complied with the specification.

Forced degradation studies were performed on naldemedine tosylate to identify potential degradation products that might be formed in the active substance, to elucidate the mechanisms of formation and evaluate the stability-indicating properties of the related substances method. Solid state samples were stored for 1 month protected from light at high temperature (in closed amber glass bottle) and high temperature and high humidity (in open amber glass bottle). The conditions examined in solution were: water (high temperature), acidic condition, (high temperature), alkaline condition (high temperature), oxidative condition (high temperature). All samples were stored for 72 hours in closed amber glass bottles, protected from light. Samples were analysed for assay and content of related substances by HPLC.

No significant changes were observed in related substances and assay in the solid state. However, naldemedine tosylate in solution was labile and the level of degradation products increased under stress conditions: light, heat, acid/base hydrolysis and oxidation. Under alkaline condition, unknown degradation products increased. The results demonstrated that the HPLC method is stability-indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is an immediate release film-coated tablet containing 200 micrograms of the active substance naldemedine tosylate.

Naldemedine tablets are formulated as yellow, 6.5 mm, round film-coated tablets debossed with the Shionogi marking above the identifier code 222 on one side and the strength, 0.2, on the other side. The qualitative and quantitative composition of the tables has been provided.

As indicated above, the form of naldemedine tosylate, used to manufacture Rizmoic is a crystalline solid with suitable solid state stability and oral bioavailability. It is classified as BCS class 3.

Risk assessments (RA) and different studies were conducted to identify the critical material attributes of the active substance. As a result, active substance related substances and particle size were classified as a CMA, and a specification limit for the particle size was established.

The potential change in polymorphic form during finished product manufacture and storage was discussed and concluded that is low given the low naldemedine content in the tablets, the direct compression method used to manufacture the tablets and the packaging precautions.

The excipients used in the tablet core are D-mannitol (diluent), croscarmellose sodium (disintegrant) and magnesium stearate (lubricant), which are all standard for pharmaceutical preparations and comply with their respective Ph. Eur. monographs. Additional specifications have been discussed and established as appropriate. The tablets are coated with a yellow non-functional film-coating consisting of hypromellose, talc and yellow ferric oxide. In-house specifications are provided for the film-coating material. Yellow ferric oxide complies with EU regulation. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. Compatibility and stability studies demonstrated that all excipients in the finished product formulation show good compatibility with the active substance. Results from risk assessment and experimental studies confirmed that there are no CMA in the excipients used.

The pharmaceutical development of the finished product included elements of science and risk-based approaches described in ICH Q8(R2) and ICH Q9. The approach consisted of following four steps;

1. Definition of Quality Target Product Profile (QTPP)

2. Determination of potential Critical Quality Attributes (p-CQAs)

3. Identification of potential Critical Material Attributes (p-CMAs) and potential Critical Process Parameters (p-CPPs) using Failure Mode Effect Analysis (FMEA): Initial risk assessment

4. Identification of CQAs, CMAs and CPPs and development of control strategies based on the results of experimental studies: Second risk assessment

The quality product profile is outlined in the table below.

Table 1 Quality target product profile

QTPP		p-CQA
Dosage form	Oral formulation, immediate release drug (Efficacy)	Dissolution
Strength	0.2 mg (Efficacy)	Assay, uniformity of dosage units
Description	Yellow, round shaped film-coated tablets debossed with trade mark and 222 on one side and 0.2 on the other side. (Ease of use, distinguishability)	Appearance
Formulation	Use of well characterized, compatible excipients (Safety, stability)	Related substances
Packaging	Bottle and blister packaging: moisture proof container (Safety, efficacy)	Related substances, water content
Manufacturing Process	Develop a robust manufacturing process. (Product quality)	Uniformity of dosage units, assay, related substances, water content, microbial, appearance, dissolution

From the results of the initial risk assessment and second risk assessment, CPPs and CMAs which have an impact on finished product quality were identified. The finished product quality attributes which are affected by CPPs and CMAs such as assay, related substances, uniformity of dosage units, appearance and water content are classified as CQAs.

An overview of the formulations used during the development program was provided. In the early clinical trials, naldemedine oral solution / suspension containing 0.01 mg to 100 mg of naldemedine as free base were used. This oral solution / suspension was prepared by the study pharmacist at the clinical site and dispensed into the subject's dose container. The tablets used for Phase 1 to Phase 2b clinical study were 0.1 mg, 1 mg, 10 mg film-coated tablets , the tablets for the Phase 3 clinical study were 0.2 mg film-coated. The formulation for the commercial product is identical to the Phase 3 clinical study formulation. The formulation used for Phase 1 to Phase 2b was changed for the Phase 3 clinical study with respect to strength, diameter, weight of core tablet, level of magnesium stearate and colour. In order to evaluate the impact of the changes, dissolution profiles for the formulation used in Phase 1 to Phase 2b were compared to dissolution profiles for the formulation used in Phase 3. Based on the results of the bioavailability study and comparative dissolution profiles, it was concluded that the impact of the formulation change on the product performance was not significant and the formulation designed for Phase 3 is suitable for use in the Phase 3 clinical program.

The manufacturing process, which was used in the early development studies and which will also be used for the commercial product is a standard direct compression method. This was selected due to the sensitivity of naldemedine to water. Since the active substance concentration in the tablets is extremely low, the process development studies at pilot scale were focused on the design of the blending process with the goal of obtaining a blend of uniform content. Appropriateness of the defined blending time at commercial scale was verified.

A holding time has been determined for the final blend manufactured at commercial size. The batch was packaged simulating actual storage conditions and tested for water content, impurities and assay. The proposed holding time of the final blend prior to compression has been demonstrated.

The applicant confirmed that the start of the shelf-life for the finished product is set in accordance with the guideline on start of the shelf-life of the finished dosage form (CPMP/QWP/072/96).

The choice of dissolution medium was based on the solubility of naldemedine tosylate, stability of solution and dissolution profiles of the tablets.

Dissolution profiles for Rizmoic 0.2 mg tablets were evaluated according to Ph. Eur. 2.9.3 in several media at different pH (ranging from pH 1.2 to 10, to include the physiological pH range). Based on the results of this study, together with the stability of naldemedine the dissolution medium was selected .During the manufacturing process development the effect of different manufacturing variables on dissolution was investigated. It was shown that none of these variables affect dissolution. This has been attributed to the high solubility of the active substance over the physiological pH range.

The tablets are packaged in an aluminium-plastic laminate (cold form foil) with a polyvinyl chloride (PVC) based heat seal coated aluminium foil (lid stock). The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product will be manufactured at the manufacturing site described in the MAA. Other sites involved in packaging, QC testing and release and their responsibilities have been described.

The manufacturing process consists of six main steps: sieving, blending, compression, coating, bulk packaging and primary packaging. Relevant information on storage and transportation of intermediate products and/or bulk ware has been presented.

The in-process control tests (IPCs), critical process parameters (CPPs) and non-critical process parameters (non-CPPs) have been defined.
Due to the low dosage the manufacturing process is considered non-standard. The manufacturing process has been validated with three consecutive validation batches covering the maximum batch size. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification (HPLC/UV), related substances (HPLC), water (Ph. Eur.), uniformity of dosage units (Ph. Eur.), dissolution test (Ph. Eur), assay (HPLC), microbial limits (Ph. Eur.).

The proposed limits have been adequately established and justified. The limits for related substances were reconsidered to reflect the level seen in batch analysis and stability studies. Moreover, a discussion on elemental impurities in line with the ICH Q3D guideline is presented. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.
Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis results are provided for three commercial scale batches and several pilot scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC /75% RH) according to the ICH guidelines were provided. The batches of Rizmoic tablets 200 micrograms are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The primary stability batches were evaluated for description, related substances, water content, disintegration, dissolution profile, assay, identification, uniformity of dosage units and microbial limits. The analytical methods used for stability testing are the same as those used for release testing, with the exception of the dissolution profile. Disintegration is not included as a release test. The methods used for disintegration and dissolution testing in the stability programme have been adequately described.

No changes were observed on description, identification, water content, uniformity of dosage units, disintegration, dissolution and microbial limits.

Although a slight increase in water content and related substances (accompanied by a decrease in assay), were observed after storage at long term and accelerated conditions, all results remained within the specification.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Tests included description, identification, related substances, water, uniformity of dosage units, disintegration, dissolution and assay. In the study samples, there was an increase in the level of some impurities .The content of naldemedine decreased. However, an increase of

degradation products in the aluminium foil covered control was not observed above the reporting threshold. Water increased, however there was a similar trend with the aluminium foil covered control.. No changes were observed in the other test items. The results of the photostability testing indicate that Rizmoic tablets 0.2 mg are susceptible to degradation when exposed to conditions of high light intensity. However, when exposed to normal light conditions during the manufacturing processes there is no evidence of photo instability.

A bulk hold study on two batches stored in LDPE bag with silica gel desiccant stored in an aluminium bag under different temperature/humidity conditions for 12 months was presented. Tests performed were description, related substances, water content, dissolution, assay and microbial limits. No significant changes were observed in the test attributes. This study demonstrated stability through 12 months of storage at ambient temperature in warehouse conditions, which supports a bulk hold time of 12 months.

A temperature cycling study was conducted to evaluate the effect of freeze-thaw on naldemedine tablets. Samples packaged in aluminium foil blisters from one primary stability batch were evaluated according toa temperature cycling protocolthree times. Tests performed were description, related substances, dissolution and assay. The amount of some degradation products increased after three temperature cycles but their values were well within the limits of the specification. No changes were observed in the other test items. This study concluded that short period temperature excursions do not have any adverse impact on the tablets packaged in aluminium blisters.

A stress stability study was also conducted in order to identify the potential degradation products of the finished product and demonstrate that the methods for related substances are stability indicating.
In the solid state samples were exposed to high temperature and humidity, high temperature and high humidity .In all conditions the samples were stored in open petri dish protected from light. The major degradation product was identified .Under high humidity condition, this product and other impurity also increased. Under high temperature and humidity condition, other impurity also increased. Under high temperature condition, unknown degradation products increased. Assay decreased under all conditions.

In the solution phase samples were exposed to oxidative, acidic and alkaline conditions. Degradation was observed under all conditions. Assay decreased under oxidative and acidic conditions.

Based on available stability data, the proposed shelf-life of 3 years stored in the original package in order to protect from light and moisture as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The major objection initially raised requesting re-definition of the proposed starting material has been adequately addressed. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The major objection initially raised requesting re-definition of the proposed starting material has been adequately addressed. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A comprehensive nonclinical development program was performed, including pharmacology, safety pharmacology, pharmacokinetics and toxicology studies, according to ICH M3 and other relevant guidelines.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro data show that naldemedine binds to both rat and human human μ-, δ-, and κ opioid receptors. The *in vitro* binding affinity of naldemedine to μ-, δ-, and κ opioid receptors is comparable between human and rats receptors. *In vitro* binding affinity data of five metabolites have shown that nor-naldemedine, naldemedine 3-G, naldemedine 6-G, and naldemedine-carboxylic acid have less potent binding affinities than naldemedine and benzamidine does not have significant binding affinities for these opioid receptors.

In vitro data show antagonistic activities of naldemedine against human μ-, δ-, and κ-opioid receptors. Nor naldemedine, naldemedine 3-G, naldemedine 6-G, naldemedine-carboxylic acid show some antagonistic activities against these opioid receptors but less potent that naldemedine. Benzamidine did not show any apparent antagonistic activities.

Agonistic activity against μ-, δ-, or κ-opioid receptor was only apparent with nor-naldemedine, the most abundant circulating metabolite in human plasma. Nor-naldemedine showed agonist activity against δ-opioid receptor with the EC50 value more than 300 fold higher than the Cmax value of nor-naldemedine at the intended clinical dose of naldemedine. All other in vitro data point toward no agonistic activity of naldemedine and it metabolites.

Naldemedine was tested for *in vitro* antagonistic and agonistic activities against rat μ-, δ-, and κ-opioid receptors. The results indicate that the functional activities of naldemedine against rat opioid receptors were comparable to those against human opioid receptors.

Data from *in vitro* binding kinetic studies of naldemedine showed slower association and dissociation kinetics to human or rat μ-opioid receptor when compared with the positive control, naloxone.

In vitro data showed concentration-dependent antagonistic action on DAMGO-induced contraction inhibition. The available data suggest that naldemedine antagonises DAMGO-induced μ-opioid receptor activation as well as morphine-, oxycodone-, hydrocodone-, or fentanyl-induced [35S]-GTPγS binding in a non-competitive manner. Naldemedine is described as a non-competitive antagonist by the Applicant.

It is acknowledged that there are circumstances in the primary pharmacology and receptor binding kinetic of naldemedine that could indicate that in the tested concentration range, naldemedine might act as a non-competitive antagonist to the μ-opioid receptor. However, the applicant determine non-competitive characteristic based solely on naldemedine not acting as a competitive antagonist – without taking into consideration that other types of binding than competitive and non-competitive also exist. It is furthermore acknowledged that due to solubility challenges, it was not possible to prepare higher concentrations of naldemedine in order to demonstrate more clearly that the curves presented in study report S-297995-EB-311-R does indeed follow a non-competitive antagonist profile. As presented in the report now, the curve fit demonstrate right-shift, but decrease of the maximum effect is more difficult to observe. The applicant also describe naldemedine as a naltrexone derivative, and naltrexone being described as a competitive antagonist, this contribute to the theory that naldemedine would also be acting as a competitive antagonist. Therefore it is concluded that naldemedine most likely is best described as a competitive antagonist.

However, no further nonclinical elaboration will be pursued, as 1) the nature of naldemedines antagonistic effect is not mentioned in the SmPC, 2) the applicant included the following sentence in the SmPC; *There is limited experience in patients treated with opioid pain medicinal product(s) at doses more than the equivalent of 400 mg of morphine. There is no experience in patients treated for constipation induced by partial opioid mu-agonists (e.g. buprenorphine).*

Naldemedine antagonises both the subcutaneously and the orally administered opioid-induced inhibition of small intestinal transit in rats. Naldemedine antagonism was more effective for oxycodone-induced constipation [ED50: 0.02 mg/kg] than for morphine-induced constipation, when the latter was administered by oral route [ED50: 0.23 mg/kg (p.o.), ED50: 0.03 mg/kg (s.c.)]. As a point of comparison, the clinical intended dose is 0.003 mg/kg. The Cmax at the clinical intended dose was similar to the Cmax at the ED50 for s.c. administered morphine and oxycodone. However with regards to the p.o. morphine, Cmax levels at ED50 were about 10-fold higher. This difference in ED50 values following subcutaneous and oral administration of morphine to naldemedine-treated animals is likely to be attributable to differences in the morphine plasma concentrations following the two routes of administration.

Secondary pharmacodynamic studies

At 10 mg/kg, opioid receptors were occupied by naldemedine in both rat cerebral cortex and thalamus 4 hours post dose. The occupancies reached 14% for a 10 mg/kg dose, which is 487x the clinical intended dose. At 3 mg/kg (146x the clinical intended dose), opioid receptors were not occupied by naldemedine in both regions, up to 24 hours post-dose.

The peripherally- and centrally-mediated withdrawal symptoms induced by naldemedine were assessed in morphine-dependent mice and rats. In mice, naldemedine caused a peripherally-mediated withdrawal symptom (diarrhea – up to 10 mg/kg). In rats, it caused peripherally-mediated withdrawal symptoms from 0.3 mg/kg and a centrally-mediated withdrawal symptom (teeth chattering) at 3 mg/kg (the highest tested dose). In ferrets 0.3 mg/kg naldemedine dosed orally completely inhibited the morphine-induced emetic responses 30 minutes to 6 hours post-dose.

In clinic, no effect has been observed on centrally-mediated analgesia. Since Naldemedine is a μ-receptor antagonist and as such, has the potential to affect centrally-mediated μ-receptor agonist activity, a

warning was included in section 4.4 of the SmPC and an anti-analgesic effect due to centrally-mediated opioid receptor antagonism is considered an important potential risk of naldemedine in the RMP (Risk Management Plan). This is only expected in patients who have disruptions to the BBB (e.g. patients with primary brain malignancies, CNS metastases or other inflammatory conditions).

Safety pharmacology programme

The safety pharmacology studies performed assessed the effects of naldemedine on CNS, cardiovascular and respiratory systems. No effects of naldemedine were observed on in the CNS study or in the respiratory study, nor in the *in vivo* cardiovascular study in telemetered dogs. However, the *in vitro* studies on repolarisation in isolated guinea pig papillary muscle, as well as the hERG study showed that naldemedine has a potential to prolong action potential in the guinea pig papillary muscle and inhibit peak tail currents in the hERG test. However, both these positive results occurred at concentrations of 30µmol/L which exceed the clinical Cmax of 2 ng/mL by far. Therefore the CHMP considers that there is no specific concern on cardiovascular function following treatment with naldemedine at the proposed clinical doses.

Abuse potential

Three animal abuse potential assessment studies, ie, a drug discrimination study in rats, a self-administration study in monkeys, and a physical dependence study in rats were conducted to evaluate the potential of naldemedine for abuse liability.

Naldemine did not show morphine-like discriminative stimulus properties in rats at doses covering the intended clinical dose of naldemedine (C_{max}, Animal to Human ratio: 7.6) and its major metabolite nor-naldemedine (C_{max}, Animal to Human ratio: 4.2). No reinforcing effect was observed in monkeys by intravenous self-administration (C_{max}, Animal to Human ratio: 27). Naldemedine did not have also physical dependence-producing potential in rats at doses higher than the intended clinical dose of naldemedine (C_{max}, Animal to Human ratio: 2884).

2.3.3. Pharmacokinetics

Quantitation of naldemedine and metabolites in plasma samples from pharmacokinetic studies and toxicity studies were determined using LC/MS/MS. The analytical methods were validated with respect to selectivity, recovery, accuracy, precision, and stability.

In rats and dogs, the pharmacokinetics of naldemedine after a single oral administration under non-fasted condition is considered to be within the range of dose-linearity up to 3 mg/kg. The pharmacokinetics of naldemedine in efficacy dose models in rats fell within the range of dose-linearity.

Naldemedine was rapidly and well absorbed after oral administration in non-fasted dogs, but less absorbed in non-fasted rats. Pharmacokinetics after oral administration were affected by the food condition in both rats and dogs. The change in pharmacokinetic profiles between non-fasted and fasted dog is not solely due to absorption as there are marked changes in parameter related to elimination of naldemedine. The changes to pharmacokinetics of naldemedine in relation to food condition are similar in rats, but less pronounced with one except that bioavailability changes in rats. The differences seen in relation for food condition in the clinical development programme were less pronounced and there were no apparent changes to CL/F and $t_{½,z}$. Thus, the changes in elimination kinetics observed in dogs and rats appear not to be relevant in humans.

Plasma protein binding is high in all species that were tested, including human. Available results indicate that naldemedine predominantly is bound to HSA in human serum. The distribution in blood cells appears to be low and similar across the tested species, including human.

Naldemedine was widely distributed into tissues of rats, and high levels of radioactivity were detected in rectal mucosa, submaxillary gland, liver, parotid gland, and harderian gland. Naldemedine was not detected in the brain.

In the nasal bone a high radioactivity was observed 1008 hours after last administration in a study with repeated oral administrations of [carbonyl-14C]-naldemedine in rats. The data presented suggests very limited or no distribution to the nasal bone via the systemic circulation and the high levels of radioactivity observed in nasal bone could be due to contamination as a result of oral administration.

After oral administration of [14C]-naldemedine to male pigmented rats, radioactivity was observed in melanin-containing tissues over somewhat longer period than in other tissues. The radioactivity in the uveal tract after administration of [oxadiazole-14C]-naldemedine or [carbonyl-14C]-naldemedine decreased with t½,z values of 309 and 447 hours, respectively. Naldemedine and its metabolites was not considered to be retained in melanin-containing tissues.

Naldemedine and its related materials crossed the placenta of pregnant rats and were also excreted into milk of nursing rats. This is reflected in the SmPC section 4.6 and 5.3.

The major metabolic pathways of naldemedine in human hepatocytes is thought to be glucuronidation at the 3- or 6-hydroxyl group in morphinan structure and N-dealkylation at methylcyclopropane group at 17-position. The major metabolizing enzymes involved seem to be CYP3A4 and UGT1A3.
Nor-naldemedine is the main circulating naldemedine metabolite in mice, rats, rabbits, dogs and humans. The plasma level of nor-naldemedine excessed 10% following repeated oral dosing in humans. Minor metabolites in human plasma following repeated dosing were naldemedine-(7R)-7-hydroxide and naldemedine 3-G. Nor-naldemedine, naldemedine 3-G, naldemedine 6-G, naldemedine carboxylic acid, naldemedine-(7R)-7-hydroxide and benzamidine are circulating metabolites identified in rats, dogs and humans. The similarity of the metabolic process observed across species supports the use of the rat and the dog for the toxicological testing.

[Oxadiazole-14C]-naldemedine is used to assess naldemedine and metabolites except naldemedine carboxylic acid whereas [Carbonyl-14C]-naldemedine is used to assess naldemedine and metabolites except benzamidine. Naldemedine and its related metabolites having [Carbonyl-14C] were considered to be mainly excreted into faeces via bile in rats and dog. Naldemedine and its related metabolites having [Oxadiazole-14C] were considered to be evenly excreted into urine and faeces in rats and mainly via faeces in dogs. Since benzamidine was observed as a major metabolite in urine after an oral administration of [Oxadiazole-14C]-naldemedine in rats and dogs, the increased radioactivity in urine seems to be due to urinary excretion of benzamidine, which was not traced by the radiolabel of carbonyl-14C.

The in vitro assessments have demonstrated that naldemedine is not a direct inhibitor or inducer of the CYP enzymes. Likewise, the in vitro assessments have demonstrated that naldemedine was not an inhibitor of the transporters tested at the concentrations achieved following treatment with naldemedine at MHRD. At 100 fold higher concentrations than the concentrations in humans following therapeutic doses, some effects does appear, however these are not considered clinically relevant due to the high exposure margins.

The major metabolite in human plasma nor-naldemedine was also investigated *in vitro* and did not show any CYP inhibition, induction or transporter inhibition at the concentrations at the MHRD.

The 1-month repeat-dose oral toxicity studies of naldemedine in rats and dogs indicate that there is no impact on hepatic drug metabolizing enzymes at the intended clinical dose (0.2 mg/day, Cmax: 2 ng/ml). Effects on CYP activities are observed at values, which are 1000-fold and 100-fold of the Cmax of naldemedine at the intended clinical dose, in rats and dogs respectively.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies were performed in rats and dog. Naldemedine was tolerated at 500 and 2000 mg/kg doses in rats, where only a decreased body weight gain was observed for males receiving 500 mg/kg/day or more, and females at the high dose of 2000mg/kg/day. In dogs, the approximate lethal dose was higher than the high dose of 1000 mg/kg naldemedine. Clinical signs related to treatment with naldemedine were a dose dependent increase in vomiting, slight decrease in body weight and increased ALP and TBILI.

Repeat dose toxicity

In the pivotal repeat-toxicity studies, in rats, the most important toxicity findings were suppression of body weight gain, salivation and prolongation of oestrous cycle. In dogs, the most important toxicity findings were vomiting/vomitus, single cell necrosis in hepatocyte with the elevation of ALT and/or ALP activity in dogs and atrophy of adipose tissue. The findings on body weight gain, salivation, vomiting/vomitus, liver and adipose tissue occurred at exposures sufficiently above the maximum human exposure and hence to be considered of little relevance to clinical use. In addition, clinical safety data do not indicate that administration of naldemedine has hepatotoxic effects on the human liver. In rats, prolongation of oestrous cycle was observed in rats at 0.3 mg/kg/day in the 1 month-repeat dose (no safety margin), but this was not observed at 1 mg/kg/day in the fertility study (safety margin of 12). In the supplemental mechanistic study, effect of naldemedine on prolactin levels was not observed at 1 mg/kg. In human, effects of naldemedine on prolactin levels were also observed, but only at high doses (≥ 10 mg/day). Based on these results, this phenomenon is not considered to be relevant in human at the clinical dose of 0.2 mg.

Genotoxicity

In the genotoxicity tests performed, Ames test, *in vitro* gene mutation in mammalian cells and *in vivo* chromosomal aberration test in rats, naldemedine did not show any potential to be genotoxic.

Carcinogenicity

In the carcinogenicity studies in rats and mice, with repeated dosing of up to 104 weeks duration at doses of up to 100 mg/kg day, no naldemedine related neoplastic findings were recorded. Based on these results, it was concluded that naldemedine does not have any carcinogenic potential.

Reproduction Toxicity

Naldemedine did not impair fertility in rats. Irregular oestrous cycles increased dose-dependently, but the irregular oestrous cycles were recovered during the pre-mating or mating periods and the females successfully copulated with the males. The AUC-based safety margins at the NOAEL were 30958x in males and 12x in females for reproductive function and 16920 x for early embryonic development.

In rabbits, an abortion, premature delivery and decreases in body weight associated with low maternal food consumption were noted in dams receiving 400 mg/kg/day of naldemedine. Decreases in body weight associated with low maternal food consumption were noted in dams receiving at least 25 mg/kg/day of naldemedine. For maternal general toxicity, the safety margin (AUC_{0-24hr}) was less than 22 (NOAELS = ≤ 25 mg/kg/day) at MHRD. For maternal reproductive function and embryo-foetal development, the safety margin (AUC_{0-24hr}) was 226 (NOAELs = 100 mg/kg/day). It is noted that the rabbit was not the most appropriate non-rodent model, as the C_{max} and AUC_{0-24hr} values of the metabolite 3-G were higher than those of naldemedine at all the tested doses (up to 31x for C_{max} and up to 42x for AUC_{0-24hr}), which is not the case in human (see chapter 2.Pharmacology). In rats, the safety margins (AUC_{0-24hr}) were 518 for maternal general toxicity (NOAEL = 10 mg/kg/day) and 23081 for maternal reproductive function and embryo-foetal development (NOAEL = 1000 mg/kg/day).

In the 30 and 1000 mg/kg/day groups, total litter loss, which was likely to be due to poor nursing such as scattering of all offspring in the cage, was observed in 5 and 3 dams, respectively. This finding was correlated with a small size of thymus in most animals (4/5 in 30 mg/kg/day group and 2/3 in 1000 mg/kg/group) and with a small size of spleen in some animals (2/5 in 30 mg/kg/day group and 1/3 in 1000 mg/kg/group). A small size of thymus has been also observed in the dam which died during parturition on Gestation Day 22 in the 1000 mg/kg/day group. The number of dead newborns was also increased on Day 4 after birth in the 30 mg/kg/day group or more. These findings could be interpreted either as stress related changes or as an exaggerated pharmacodynamics action and were not observed in the 1 mg/kg/day group. The safety margin (AUC_{0-24hr}) for maternal general toxicity, maternal reproductive function, and development of the subsequent generation is 12 and as such the findings are considered not clinically relevant.

Naldemedine is subject to an approved Paediatric Investigational Plan (EMEA-001893-PIP01-15). The juvenile toxicity studies have identified new histopathologic findings in mammary glands and in ovaries, at all doses ≥ 1 mg/kg/day. A NOAEL could not be defined. The lowest dose tested corresponds to an exposure margin of at least 6 for the clinical intended dose in adults of 200 µg. These microscopic findings may be related with the observed disturbance of oestrous cycle activity and earlier vaginal opening. This is appropriately reflected on the SmPC. The mechanism underlying these findings in rats, as well as their clinical relevance, are unknown.

Local Tolerance

In support of this application, stand-alone local tolerance studies are not expected, as the local tolerance following oral administration is sufficiently addressed in the repeat-dose toxicity studies.

Other toxicity studies

Phototoxicity

Naldemedine did not show any phototoxic potential in the in vivo study performed in hairless mice. However, no in vitro testing appears to have been performed prior to the in vivo study (as per ICH S10 guidance). As the phototoxicity study has been performed prior to implementation of ICH S10, this is acceptable.

Immunotoxicity and antigenicity

In repeat-dose toxicities studies, decreased in thymus weight were observed in rats (6-month study) and in dogs (1-, 3- and 9-month studies). In rats, this finding was not accompanied by histopathological lesions and was considered to be non-adverse. In dogs in most cases, the decrease in thymus weight was accompanied with gross finding (small size) and with histopathological lesions (atrophy, decreased in

number of lymphocytes in the cortex and/or appearance of lymphatic follicle in the medulla). These findings were considered not to be treatment-related since it was not dose-related and clear dose-relationship was not evident in the related thymic weights or histopathological atrophy of the thymus. These findings could be also stress-related immune changes observed in standard toxicity studies (e.g. by exaggerated pharmacodynamics action). As recommended in the ICH S8 guidelines, these findings call for additional nonclinical immunotoxicity testing. As such, the Applicant conducted an immunotoxicity study (T-cell dependent antibody formation) in rats (Dose: 0 [control], 30, 100, and 1000 mg/kg/day), in which naldemedine had no effects on T-cell dependent antibody formation. No further nonclinical immunotoxicity testing is needed.

Metabolites and impurities

No specific studies to investigate the toxicity of naldemedine metabolites have been conducted. Nor-naldemedine is the main circulating naldemedine metabolite across species. The following minor metabolites, naldemedine 3 G, naldemedine 6-G, benzamidine and naldemedine carboxylic acid are present at low levels. The metabolites are considered to be adequately qualified in the nonclinical toxicology studies conducted.

Bacterial reverse mutation (Ames) testing was performed for the identified potential impurities that may arise during manufacturing. None of the Ames tests performed was positive.

Additional mechanistic studies

Two additional mechanistic studies clearly showed that prolactin level was increased after naldemedine administration. The fluctuations of the levels observed for the other hormones (progesterone, estradiol, luteinizing hormone and follicular stimulating hormone) were not clearly related to naldemedine and could represent a secondary effect of the increase level of prolactin or of the irregular oestrous cycle. The plasma prolactin level in female rats was increased by oral administration of naldemedine at 10 mg/kg or more, but no effect was observed at 1 mg/kg. There was no dose-dependency, as the degree of the increase (around 22-fold) was comparable among the 10, 100, and 1000 mg/kg groups. The release of prolactin by naldemedine could be related to the stimulation of the hypothalamic dopaminergic neurons. In an single dose study in rats (3, 10 and 30 mg/kg), naldemedine was present in the brain from 4 hours post-dose and occupancies of naldemedine against opioid receptors was also observed in dose-dependent manner. These data supported the possibility that naldemedine has effects on hypothalamic-pituitary axis at ≥ 10 mg/kg. The second possible mechanism is that naldemedine stimulates prolactin release via the ovarian function in rats, as prolactin increased has been observed only in females. It is known that oestrogen, which is mainly secreted by the ovary, stimulates prolactin release by enhancing the growth of prolactin producing cells and also stimulates prolactin production. However, the exact mechanism of prolactin increase by naldemedine has not been clearly elucidated by mechanistic studies. Taking into account that the effects on oestrous cycle observed in rats are considered the consequence of prolactin increase, that the mechanism of prolactin increase has not been elucidated and that in human prolactin increase has been observed at higher doses, the applicant commits to follow up on prolactin-related effects in humans in the post-authorisation setting.

2.3.5. Ecotoxicity / environmental risk assessment

Table 2 Summary of main study results

Substance (INN / Invented Name): Naldemedine			
CAS-number (if available): 1345728-04-2 (tosylate), 916072-89-4 (free base)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log d_{ow}	OECD107	Ph 4 – 1.2 Ph 7 – 2.2 Ph 9 – 2.1	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log d_{ow}	1.2 – 2.2	not B
	BCF	-	-
Persistence	DT50 or ready biodegradability	-	-
Toxicity	CMR		not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.001	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)

Naldemedine PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Therefore naldemedine is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The Applicant has presented a comprehensive non-clinical study package demonstrating naldemedines effect in preventing opiod-induced constipation, in both mice, rats and ferrets.

Naldemedine was tested for in vitro antagonistic and agonistic activities against rat µ-, δ-, and κ-opioid receptors. The results indicate that the functional activities of naldemedine against rat opioid receptors were comparable to those against human opioid receptors.

Naldemedine is described as a non-competitive antagonist by the Applicant. However, upon further review of the provided nonclinical studies (studies S-297995-EB-331-R and R-297995-EF-013-R) it is unclear what the nature of antagonism of naldemedine is.The applicant determines non-competitive characteristic based solely on naldemedine not acting as a competitive antagonist – without taking into consideration that other types of binding than competitive and non-competitive also exist. Naldemedine is also described as a naltrexone derivative, and naltrexone being a competitive antagonist, contributes to the theory that naldemedine would also be acting as a competitive antagonist. Therefore it is concluded that naldemedine most likely is best described as a competitive antagonist. However, no further nonclinical elaboration will be pursued, as 1) the nature of naldemedines antagonistic effect is not mentioned in the SmPC, 2) the applicant included the following sentence in the SmPC; *There is limited experience in patients treated with opioid pain medicinal product(s) at doses more than the equivalent of 400 mg of morphine. There is no experience in patients treated for constipation induced by partial opioid mu-agonists (e.g. buprenorphine).*

The peripherally- and centrally-mediated withdrawal symptoms induced by naldemedine were assessed in morphine-dependent mice and rats. In mice, naldemedine caused a peripherally-mediated withdrawal symptom (diarrhoea – up to 10 mg/kg). In rats, it caused peripherally-mediated withdrawal symptoms from 0.3 mg/kg and a centrally-mediated withdrawal symptom (teeth chattering) at 3 mg/kg (the highest tested dose). In ferrets 0.3 mg/kg naldemedine dosed orally completely inhibited the morphine-induced emetic responses 30 minutes to 6 hours post-dose. In clinic, no effect has been observed on centrally-mediated analgesia. Since Naldemedine is a μ-receptor antagonist and as such, has the potential to affect centrally-mediated μ-receptor agonist activity, a warning was included in section 4.4 of the SmPC and an anti-analgesic effect due to centrally-mediated opioid receptor antagonism is considered an important potential risk of naldemedine in the RMP (Risk Management Plan). This is only expected in patients who have disruptions to the BBB (e.g. patients with primary brain malignancies, CNS metastases or other inflammatory conditions).

No safety concerns were revealed in the safety pharmacology studies performed, nor did naldemedine show any potential for abuse in the nonclinical studies performed.

Pharmacokinetics after oral administration was affected by the food condition in both rats and dogs. However, as there was no clinically significant food effect shown in the clinical setting no precautions on food effects are considered necessary.

Naldemedine was widely distributed into tissues of rats, and high levels of radioactivity were detected in rectal mucosa, submaxillary gland, liver, parotid gland, and harderian gland. Naldemedine was not detected in the brain.

The toxicity of naldemedine was primarily studied in rats and dogs, but mice and rabbits were used for carcinogenicity and reproductive toxicity studies respectively. In the rat fertility and early embryonic development study, prolongation of dioestrous phase was observed at 10 mg/kg/day and above, but was not observed at 1 mg/kg/day (12 times the exposure [$AUC_{0\text{-}24hr}$] in humans at an oral dose of 200 micrograms). The effect on oestrous cycle is not considered clinically relevant at the proposed therapeutic dose. No adverse effects were observed in male or female fertility and reproductive performance up to 1000 mg/kg/day *(in excess of 16,000 times the exposure [$AUC_{0\text{-}24hr}$]* in humans at an oral dose of 200 micrograms). This information has been included in the SmPC.

In the pre- and postnatal development study in rats, one dam died at parturition at 1000 mg/kg/day, and poor nursing, suppression of body weight gain and decrease in food consumption were noted at 30 and 1000 mg/kg/day. Decreases in the viability index on Day 4 after birth were noted at 30 and 1000 mg/kg/day and low body weights and delayed pinna unfolding were noted at 1000 mg/kg/day in pups. There was no adverse effect on pre- and postnatal development at 1 mg/kg/day (12 times the exposure [$AUC_{0\text{-}24hr}$] in humans at an oral dose of 200 micrograms). This information has been included in the SmPC.

Placental transfer of [carbonyl-^{14}C]-naldemedine-derived radioactivity was observed in pregnant rats. [Carbonyl-^{14}C]-naldemedine-derived radioactivity was excreted into milk in lactating rats. The use of naldemedine during pregnancy is therefore not recommended in the SmPC as it may precipitate opioid withdrawal in a foetus due to the immature foetal blood brain barrier. Also, as there is a theoretical possibility that naldemedine could provoke opioid withdrawal in a breast-fed neonate whose mother is taking an opioid receptor agonist the SmPC recommends not to use naldemedine during breast-feeding.

In juvenile toxicity studies in rats, at the same dose levels, exposure in juvenile animals (PND 10) was increased compared to adult animals (1.5 to 3-fold). Novel histopathology findings were observed at all doses tested in female rats in mammary glands (increased incidences in lobuloalveolar hyperplasia) and in ovaries (tertiary follicles/luteal cysts) in addition to irregular oestrous cycles and vaginal mucification

already observed in adult animals (the lowest dose tested corresponded to an exposure margin of 6 or more, depending on the age of the pups). Changes indicative of an early onset of sexual maturity including 3-days earlier vaginal opening were also observed, but only at high exposures considered sufficiently in excess of the maximum human exposure at an oral dose of 200 micrograms.

Two additional mechanistic studies clearly showed that prolactin level was increased after naldemedine administration in female rats. Oestrus cycle prolongation was observed in female rats at all dose levels. The exact mechanism of prolactin increase by naldemedine has not been clearly elucidated. Taking into account that the effects on oestrous cycle observed in rats are considered the consequence of prolactin increase that the mechanism of prolactin increase has not been elucidated and that in human prolactin increase has been observed at higher doses the applicant will be monitor prolactin-related effects in humans in the post-authorisation setting and cases reporting relevant MedDRA PTs (Blood prolactin increased, Blood prolactin abnormal, Hyperprolactinaemia) will be followed up for further information.

Carcinogenicity or genotoxicity studies did not show any relevant findings.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical profile of naldemedine was established in a comprehensive investigational program that included studies of *in vitro* and *in vivo* pharmacology, safety pharmacology, pharmacokinetics and toxicity. Non clinical studies do not reveal special hazard for humans.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant. During a routine GCP inspection one site from the pivotal study V9235 was excluded due to suspected data manipulation and due to further critical GCP findings the applicant was requested to submit a re-analysis of efficacy data of the three pivotal studies V9231, V9232 and V9235. None of the above actions changed the overall results of the studies.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The clinical program for the treatment of OIC in subjects with chronic non-cancer pain encompasses of 2 phase 2 studies (V9214 and V9221) and 3 phase 3 studies (V9231, V9232 and V9235) plus 2 phase 3 supportive studies (V9238 and V9239) and for the treatment of OIC in subjects with cancer encompasses of 1 phase 2 study (V9222) and 2 phase 3 studies (V9236 and V9237) as illustrated in the table below:

- Tabular overview of clinical studies

Type of Study (Location)	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Actual (Planned)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 1 Dose escalation, PK (5.3.3.1)	0824V9211	To evaluate the safety, tolerability, and pharmacokinetics of a single dose of naldemedine in healthy Japanese adult male subjects	Single-dose, randomized, double- blind, dose-escalation study	Naldemedine 0.1, 0.3, 1, 3, 10, 30 mg or placebo Single dose Oral, Solution, Naldemedine 100 mg or placebo Single dose Oral, Suspension	56 (56); naldemedine 42, placebo 14	Healthy Japanese male subjects	One day	Complete; Full
Phase 1 BA and Food effect, PK (5.3.1.1)	0909V9212	Comparative Bioavailability of 10 mg Tablet and Food Effect Study in Healthy Japanese Subjects	Open-label, randomized, three-period crossover study	Naldemedine tosylate 10 mg, Oral, Solution Naldemedine tosylate 10 mg, Oral, Tablets, fasted Naldemedine, Oral, Tablets, fed	15 (15)	Healthy subjects	3 non-consecutive days	Complete; Full
Phase 1 Dose escalation, PK (5.3.3.1)	0917V9213	To evaluate the safety, tolerability, and pharmacokinetics of multiple oral doses of naldemedine in healthy Japanese adult males	Double-blind, randomized, placebo- controlled study	Naldemedine 3, 10, 30 mg, placebo Once daily administration x 10 days Oral Naldemedine 3 and 10 mg tablets Matching placebo	36 (36); naldemedine 27, placebo 9	Healthy adult male subjects	10 days	Complete; Full
Phase 1 Mass balance, PK (5.3.3.1)	1016V9215	To assess the mass balance of naldemedine in healthy subjects To characterize the metabolism and routes of elimination for naldemedine and naldemedine metabolites	Open-label, non-randomized, absorption, metabolism, and excretion study	[Oxadiazole-^{14}C]-naldemedine 2 mg 14 [Carbonyl- C]-naldemedine 2 mg Single dose Oral Solution	12 (12); 6 per group	Healthy adult male subjects	One day	Complete; Full
Phase 1 Extrinsic Factor PK (DDI) (5.3.3.4)	1202V9218	To determine the effect of a single dose of cyclosporine on naldemedine pharmacokinetics	Open-label, randomized, 2-period crossover study	Naldemedine 0.4 mg Single dose Oral Tablet (0.1 mg) Cyclosporine 600 mg Single dose Oral Solution	14 (14)	Healthy adult male subjects	Two non-consecutive days	Complete; Full

Type of Study (Location)	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Actual (Planned)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 1 PK/PD (5.3.4.1)	1101V9216	To evaluate the efficacy of a single oral dose of naldemedine for the reduction of opioid-induced nausea	Randomized, double-blind, placebo-controlled, parallel-group	Naldemedine 0.1, 1, 10 mg, placebo Single doses Oral Naldemedine 0.1, 1, 10 mg tablets Matching placebo	80 (80); naldemedine 60, placebo 20)	Healthy adult subjects	One day	Complete; Full
Phase 1 PK/PD (TQTc) (5.3.4.1)	1204V9219	To evaluate the effect of naldemedine on the QT interval	Randomized, double- blind, placebo- and positive-controlled, 4- period , crossover study	Naldemedine 0.2, 1 mg Single dose Oral Tablet (0.2 mg) Moxifloxacin 400 mg Single dose Oral Tablet (400 mg) Matching placebo to naldemedine	55 (48); naldemedine 0.2 mg 51, 1 mg 48, placebo 45	Healthy male and female subjects	4 non-consecutive days of single doses	Complete; Full
Phase 1 BA/FE for to-be-marketed formulation, PK (5.3.1.2)	1311V921A	To evaluate the relative bioavailability and food effect of the to-be-marketed tablet formulation of naldemedine in healthy subjects	Open-label, randomized, 3-period crossover study	Naldemedine 0.2 mg (2 x 0.1 mg), fasted Naldemedine 1 x 0.2 mg fasted) Naldemedine 1 x 0.2 mg, fed Oral	18 (18)	Healthy adult subjects	3 non-consecutive days	Complete; Full
Phase 1 Intrinsic Factor PK (Renal impairment) (5.3.3.3)	1401V921B	To evaluate the effect of impaired renal function on naldemedine pharmacokinetics	Open-label, non-randomized study	Naldemedine 0.2 mg Single dose Oral Naldemedine 0.2 mg tablet	38 (40); 8 subjects with mild, moderate renal impairment and ESRD requiring dialysis 6 subjects with severe renal impairment	Subjects with mild, moderate, severe renal impairment and ESRD requiring hemodialysis Healthy (gender, age, BMI)- matched control subjects (to subjects with moderate renal impairment	Mild, moderate or severe renal impairment: One day ESRD requiring hemodialysis: 2 non-consecutive days	Complete; Full

Type of Study (Location)	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Actual (Planned)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 1 Intrinsic Factor PK (Hepatic impairment) (5.3.3.3)	1402V921C	To evaluate the effect of impaired hepatic function on naldemedine pharmacokinetics	Open-label, non-randomized study	Naldemedine 0.2 mg Single dose Oral Naldemedine 0.2 mg tablet	24 (24); 8 subjects per cohort	Subjects with mild or moderate hepatic impairment Healthy (gender, age and BMI)- matched control subjects (matched to subjects with mild hepatic impairment	One day	Complete; Full
Phase 1 Extrinsic Factor PK (DDI) (5.3.3.4)	1403V921D	To evaluate the effect of repeated administration of rifampin 600 mg on the pharmacokinetics (PK) of a single dose of naldemedine 0.2 mg compared with a single dose of naldemedine 0.2 mg administered alone, in healthy adult subjects.	Open-label, one-sequence, 2-period, crossover, drug-drug interaction study	Naldemedine 0.2 mg Single dose Oral Tablet (0.2 mg) Rifampin 600 mg Daily administration x 17 days Oral Capsule (300 mg)	14 (14)	Healthy male and female subjects	Two non-consecutive days of single doses of naldemedine and 17 consecutive days of rifampin	Complete; Full
Phase 1 Extrinsic Factor PK (DDI) (5.3.3.4)	1502V921E	To evaluate the effect of repeated administration of itraconazole 200 mg or fluconazole 200 mg on the pharmacokinetics of a single dose of naldemedine 0.2 mg compared to a single dose of naldemedine 0.2 mg administered alone, in Japanese healthy adult subjects	Open-label, one-sequence, 2-period, crossover, drug-drug interaction study	Naldemedine 0.2 mg Single dose Oral Tablet (0.2 mg) Itraconazole 200 mg (20 mL) BID x 1 day, QD x 5 days Fluconazole 400 mg x 1 day, 200 mg x 5 days Oral Itraconazole Solution (Itrizole® Oral Solution 1%) Fluconazole Capsule (100 mg)	28 (28) total (itraconazole, 14; fluconazole, 14)	Healthy subjects (male and female)	Two non-consecutive days of single doses of naldemedine and 4 consecutive days of itraconazole or fluconazole	Complete; Full

Type of Study (Location)	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Actual (Planned)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 2a (5.3.5.1)	1007V9214	To evaluate the safety of single doses of oral naldemedine in subjects physically dependent on opioids	Randomized, double-blind, placebo-controlled, dose escalation	Naldemedine 0.01 and 0.03 mg Oral solution Oral Naldemedine 0.1, 0.3, 1, 3 mg Naldemedine 0.1 mg and 1 mg tablets Oral Matching placebo tablets and oral solution	72 (72)	Patients with chronic non- cancer pain, OBD, and opioid physical dependence	One day (Single dose administration)	Complete; Full
Phase 2b Efficacy (5.3.5.1)	1107V9221	To evaluate the efficacy and safety of naldemedine for the treatment of OIC patients with non-cancer chronic pain	Randomized, double- blind, placebo- controlled, parallel- group study	Naldemedine 0.1, 0.2 and 0.4 mg; Oral Naldemedine 0.1 and 0.2 mg tablets Matching placebo	244 (240)	Patients with chronic non- cancer pain and OIC	28 days	Complete; Full
Phase 3 Efficacy (5.3.5.1)	1314V9231	To evaluate the efficacy and safety of naldemedine for the treatment of OIC patients with non-cancer chronic pain	Randomized, double- blind, placebo- controlled, parallel- group study	Naldemedine 0.2 mg tablets Naldemedine 0.2 mg , QD Oral Matching placebo	547 (540)	Patients with chronic non- cancer pain and OIC	12 weeks	Complete; Full
Phas 3 Efficacy (5.3.5.1)	1315V9232	To evaluate the efficacy and safety of naldemedine for the treatment of OIC patients with chronic non-cancer pain	Randomized, double- blind, placebo- controlled, parallel- group study	Naldemedine 0.2 mg tablets Naldemedine 0.2 mg , QD Oral Matching placebo	553 (540)	Patients with chronic non- cancer pain and OIC	12 weeks	Complete; Full
Phase 3 Safety (5.3.5.1)	1326V9235	To evaluate the long-term safety of naldemedine for the treatment of OIC in patients with chronic non-cancer pain	Randomized, double- blind, placebo- controlled, parallel- group study	Naldemedine 0.2 mg tablets Naldemedine 0.2 mg , QD Oral Matching placebo	1246 (1200)	Patients with chronic non- cancer pain and OIC	52 weeks	Complete; Full
Phase 2b Efficacy (5.3.5.1)	1108V9222	To evaluate the efficacy and safety of naldemedine for the treatment of OIC in cancer patients	Randomized, double- blind, placebo- controlled, parallel- group study	Naldemedine tosylate 0.1 and 0.2 mg tablets Naldemedine 0.1, 0.2 and 0.4 mg; Matching placebo	227 (212 – 230)	Patients with cancer and OIC	14 days	Complete; Full

Type of Study (Location)	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Actual (Planned)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3 Efficacy (5.3.5.1)	1331V9236	To evaluate the efficacy and safety of naldemedine for the treatment of OIC in Japanese cancer patients	Randomized, double- blind, placebo- controlled, parallel- group study	Naldemedine 0.2 mg tablets Matching placebo	193 (190)	Patients with cancer and OIC	14 days	Complete; Full
Phase 3 Safety (5.3.5.2)	1332V9237	To evaluate the long-term safety of naldemedine in cancer patients with OIC	Open-label study	Naldemedine 0.2 mg tablets	131 (100)*	Patients with cancer and OIC	12 weeks	Complete; Full
Phase 3 Safety (5.3.5.2)	1336V9238	To evaluate the long-term safety of naldemedine in for the treatment of OIC in Japanese patients with chronic non-cancer pain	Open-label study	Naldemedine 0.2 mg tablets	43 (40)	Patients with chronic non-cancer pain and OIC	48 weeks	Complete; Full
Phase 3 Safety (5.3.5.2)	1339V9239	To evaluate the long-term safety of naldemedine for the treatment of OIC in	Open-label study	Naldemedine 0.2 mg tablets	10 (10)	Patients with chronic non-cancer pain and OIC	48 weeks	Complete; Full

* 100 subjects who completed 12 weeks treatment

The clinical pharmacology programme for naldemedine consisted of 12 Phase 1 studies conducted in healthy subjects and in subjects with hepatic or renal impairment. The PK of naldemedine was also determined in 3 Phase 2 studies in subjects with OBD, subjects with chronic non-cancer pain and OIC, and in subjects with cancer and OIC. In addition, a popPK analysis was performed.

Different formulations were used throughout clinical development: naldemedine oral solution or suspension in the first clinical trials, followed by 0.1, 1 and 10 mg dose phase 1 to phase 2 tablets and finally the phase 3 immediate-release tablet (identical to the commercial formulation) containing 0.2 mg of naldemedine. Based on the 90% CI for AUC of naldemedine, bioequivalence was concluded between the oral solution and the phase 1/2 tablet formulation and between the two tablet formulations. The small changes in Cmax (up to 13%) were not considered to be clinically relevant.

The bioanalytical reports for analytical methods used in each study were provided.

The validation of HPLC methods for the determination of naledemedine and its metabolites and other co-administered drugs was carried out at various analytical laboratories. The characteristics of linearity, within- and between-run accuracy and precision, recovery, selectivity, sensitivity, dilution integrity, matrix effect, hemolysis effect, re-injection reproducibility and stability have been validated and all validation reports were also provided.

2.4.2. Pharmacokinetics

Absorption

Naldemedine was rapidly absorbed with Tmax attained at 0.5h to 0.75h after single doses of 0.1 to 100 mg and after daily doses of 3, 10 and 30 mg for up to 28 days of naldemedine. Geometric mean naldemedine Cmax and AUC0-inf were 3.07 ng/mL and 23.79 ng·hr/ml, respectively, after a single 0.2 mg dose of the naldemedine commercial formulation in the fasted state.

The potential of naldemedine as a substrate of efflux transporters was also investigated using Caco-2 cells. The efflux ratio decreased significantly in the presence of P-gp inhibitors, but did not decrease when BCRP function was down-regulated. Therefore, it was concluded that naldemedine is a P-gp substrate, but not a BCRP substrate.

Concomitant food intake reduced the maximum plasma concentration after a single 0.2 mg dose by 35%, delayed time to Cmax from 0.75 hours to 2.5 hours, but did not influence AUC. These small differences in the Cmax and Tmax of naldemedine were not considered to be clinically meaningful. Furthermore, in the Phase 3 studies, naldemedine was administered without regard to food. Hence, it is reported in the SmPC that naldemedine can be taken with or without food.

No absolute bioavailability study was conducted. The major metabolites detected in faeces and urine (benzamidine and carboxylic acid) are assumed to be formed by enterobacteria prior to reaching systemic circulation, but the possibility that naldemedine is also metabolized to nor-naldemedine (or other metabolites) in the intestine and liver prior to reaching systemic circulation is still remained. The available data only allow a rough estimation of the absolute bioavailability.

Distribution

In vitro studies showed that the plasma protein binding of naldemedine is relatively high with binding of 93.2% to 94.2%, which was independent of the concentration. This is in line with the unbound fraction data observed in vivo in patients with normal and impaired renal and hepatic function. Naldemedine seems to be predominantly bound to human serum albumin and to a lesser extent to α1-acid-glycoprotein and γ-globulin.

The blood-to-plasma ratio was 13.5 to 16.3% in vitro, suggesting that naldemedine does not associate with the red blood cells to a meaningful extent. The apparent volume of distribution during the terminal phase (Vz/F) in healthy subjects was 155 L.

Elimination

The apparent terminal elimination half-life of naldemedine was approximately 11 hours and apparent clearance (CL/F) was 8.41 L/h after a single 0.2 mg dose of the to-be-marketed formulation in healthy subjects.

Naldemedine was not found to be a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, or OAT3 when incubating transporter-transfected HEK cells with 0.5 and 2 µM naldemedine. Of note, no involvement of renal uptake transporters was shown, although the renal clearance of naldemedine suggests involvement of active secretion.

Naldemedine is extensively metabolized in the liver and by enterobacteria after oral administration. *In vitro* experiments with cryopreserved human hepatocytes and human liver microsomes indicated that naldemedine is primarily metabolised by CYP3A4 to form nor-naldemedine, which is in line with *in vivo* results following administration of the CYP3A4 inducer rifampicin and the CYP3A4 inhibitor itraconazole (see further). UGT1A3 was found to mediate naldemedine 3-G and naldemedine 6-G formation. Benzamidine, the major metabolite in urine and faeces, was not detected *in vitro*, which supports the assumption that the oxadiazole ring of naldemedine is cleaved by enterobacteria forming benzamidine and naldemedine-carboxylic acid.

Since naldemedine is cleaved by enterobacteria, two different labels were used in the mass balance study (Oxadiazole-^{14}C and Carbonyl-^{14}C). Following oral administration of a single 2 mg dose of radio-labelled naldemedine, the main component in plasma was identified as naldemedine, whereas the systemic exposure of nor-naldemedine and naldemedine 3-G was 9% to 13% and 1% to 2%, respectively, of that of naldemedine. None of the metabolites contributed to > 10% of total plasma radioactivity and no metabolites are expected to contribute substantially to the pharmacological effect (see NC AR). A longer half-life of total plasma radioactivity than for parent compound was observed and a mean fraction of 35 to 26% of the radioactivity in the pooled plasma samples remained unextracted. A longer half-life of total plasma radioactivity vs. parent could indicate circulating metabolite(s) with a longer half-life than parent and/or radioactivity associated with binding to plasma proteins or other proteins. The applicant concluded that it is unlikely that the longer t½,z of radioactivity in plasma is due to covalent binding of naldemedine and its metabolites to plasma proteins, but suggests that the longer half-life of total plasma radioactivity is due to nor-naldemedine (longer t½,z compared to parent) which is not a reactive metabolite. Indeed,

the t½,z of total radioactivity (i.e 20.4 h), although longer than that of naldemedine, is still relatively short and substantially shorter compared to compounds known to covalently bind to plasma proteins. The incomplete extraction recovery of radiolabelled material from plasma, which increases over time, was not discussed by the applicant. However, it seems most likely that (unquantified) minor secondary metabolites with a longer t½,z than naldemedine further contribute to the longer t½,z of radioactivity in plasma. Overall, taken into account the relatively short t½,z of total radioactivity and the observed safety profile of naldemedine, no further investigations are considered necessary.

The urinary excretion profiles were similar after [oxadiazole-^{14}C]- or [carbonyl-^{14}C]-naldemedine administration showing renal elimination of naldemedine (20% of dose) and benzamidine being the major metabolite in urine (30% of dose). For the oxadiazole labelled naldemedine, 57.3% and 34.8% of the administered dose was excreted in urine and faeces, respectively, with an overall recovery of total radioactivity of 92%, and, for the carbonyl labelled naldemedine, 20.4% and 64.3% of the administered dose was excreted in urine and faeces, respectively, with an overall recovery of total radioactivity of 85%. This is not in accordance with the recommendations of the Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev. 1 Corr.*). Additionally, for the carbonyl labelled naldemedine, only 51.9 % of the dose could be profiled, which is less than 80% of the recovered radioactivity. According to the Applicant, the lower recovery after a single oral administration of [carbonyl-14C]-naldemedine is due to sustained excretion of radioactivity in faeces at the time of discharge of subjects. Still according to the Applicant, this might be due to enterohepatic circulation of a large number of supposed minor metabolites having morphinan skeleton since enterohepatic circulation has been reported for drugs having morphinan skeleton. This hypothesis is considered plausible. Furthermore, lower recovery of radioactivity after administration of [carbonyl-14C]-naldemedine is in line with findings for compounds predominantly excreted in faeces (Roffey et al., 2007), which is the case for naldemedine. Overall, as the main excretion route and metabolic pathways have been identified, the applicant's conclusion that lower than expected recovery of total radioactivity is not considered to have a substantial impact on the conclusion of the human mass balance study is agreed upon.

The proposed biotransformation pathway of naldemedine is presented in the figure below:

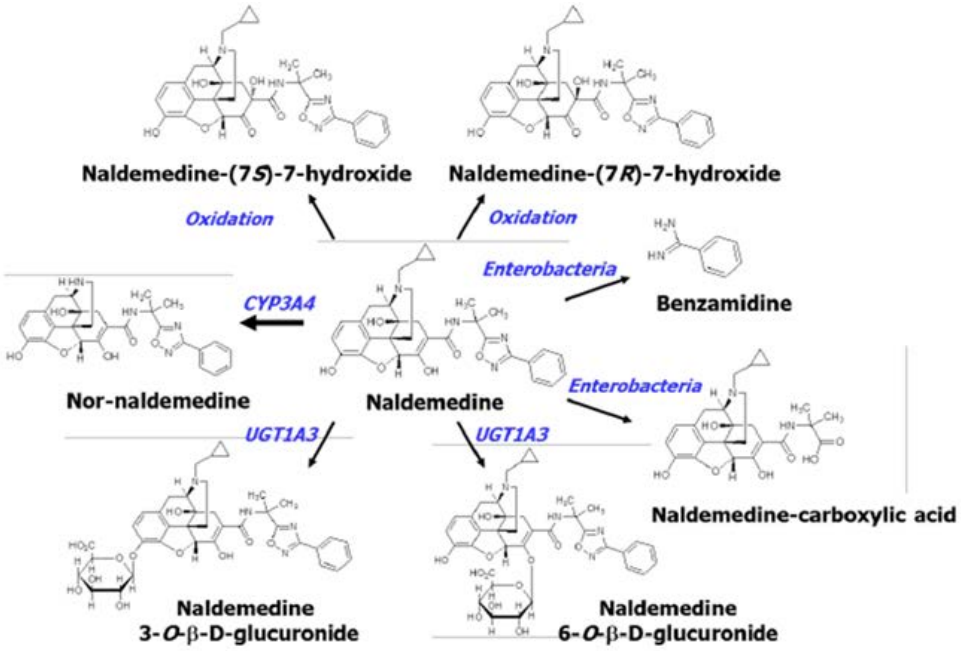


Figure 2 Proposed Metabolic Pathway of Naldemedine

The structure of naldemedine incorporates four chiral centers. Isomers of naldemedine are detected using reversed phase HPLC analysis methods because naldemedine is not an enantiomer but a diastereomer. However, no isomers of naldemedine were detected in plasma of rats, dogs, and humans. In addition, all the metabolites detected in the *in vivo* metabolic profiling of rats, dogs and humans maintained the same stereochemistry of four chiral centres as that of naldemedine, suggesting that the four chiral centres in the structure of naldemedine are unlikely to be potential metabolic sites. Furthermore, there have been no reports of *in vivo* interconversion for naltrexone and oxycodone which have a similar skeleton to naldemedine. Based on these observations and information, in vivo interconversion of naldemedine is not considered to occur.

Dose proportionality and time dependencies

Linearity/Non-linearity

Naldemedine showed dose-proportional PK after single and multiple dose administration, both in healthy volunteers as in patients. Dose-proportionality is adequately described in the SmPC.

A slight accumulation (maximal 1.3-fold) was reported for Cmax and AUC of naldemedine after once daily administration for 10 days in healthy volunteers and for 28 days in patients with non-cancer pain and OIC. Pharmacokinetic steady state was attained approximately 2 days after the start of multiple dose administration.

Intra- and inter-individual variability

A modest inter-individual variability has been noted for naldemedine. Intra- and inter-individual variability is moderate with CV% of 25-38 for the principal PK parameters.

Pharmacokinetics in target population

Population pharmacokinetic analyses

A population PK analysis to evaluate the effects of influencing factors on the PK of naldemedine was performed using 8146 naldemedine plasma concentrations from 949 subjects in a pooled dataset from 10 Phase 1, 3 Phase 2, and 5 Phase 3 studies in healthy subjects, subjects with chronic non-cancer pain and OIC, subjects with cancer and OIC, subjects with renal impairment, and subjects with hepatic impairment [Studies V9211, V9213, V9215, V9218, V9219, V921A, V921B, V921C, V921D, V921E, V9214, V9221, V9222, V9231, V9232, V9236, V9238 and V9239].

Nonlinear mixed-effects modelling was performed using NONMEM®. A two-compartment model with first-order absorption and absorption lag time was used as a structural pharmacokinetic model. An exponential error model was used for inter-individual variability and proportional error model was used for intra-individual variability.

For model building, age, body weight, BMI, gender (male, female), albumin, AST (aspartate aminotransferase), ALT (alanine aminotransferase), total bilirubin, CLcr, race/ethnicity (“White” or “non-White”, “Japanese” or “non-Japanese”, “Hispanic or Latino” or “Not Hispanic or Latino”), health status (healthy subjects/subjects with chronic non-cancer pain and OIC/subjects with cancer and OIC) and dosing conditions (dosing in the fasted/fed state, with/without concomitant use of P-gp/CYP3A inhibitor) were tested as a covariate on apparent total clearance (CL/F). Age, body weight, BMI, gender, race/ethnicity, health status, and dosing conditions were tested as a covariate on apparent distribution volume of central compartment (Vc/F). Age, gender, health status and dosing conditions were tested as a covariate on Ka (absorption rate constant). The effect of concomitant use of CYP3A inducers was not tested because there were few subjects included in the population pharmacokinetics with concomitant

use of CYP3A inducers in Phase 2 and Phase 3 studies (n=10 for strong CYP3A inducer; n=6 for moderate CYP3A inducer) [Study S-297995-CB-318-N].

After model building, Age, CLcr, race (White or non-White) and Gender were suggested to be covariates on CL/F, Body weight, health status (healthy subjects, subjects with chronic non-cancer pain and OIC, or subjects with cancer and OIC) and food condition (fasted or fed) were suggested to be covariates on Vc/F, and Age was suggested to be a covariate on Ka, respectively.

The effects of selected covariates (ie, age, creatinine clearance [CLcr], race, gender, body weight, health status [healthy subjects, subjects with chronic non-cancer pain and OIC, or subjects with cancer and OIC] and food condition [fasted, fed]) on the mean (±SD) Bayesian AUC and Cmax estimates were evaluated. These covariates selected were not considered to provide clinically meaningful pharmacokinetic differences and no dose adjustment is required for these factors.

The table below summarises the final model parameter estimates as well as bootstrap confidence intervals.

Table 3 Population PK Parameter Estimates for the Final Model

	Units	Estimate	Shrinkage (%)	95 % Confidence Interval			Median and 95 % Confidence Interval for Bootstrap estimates			
Pharmacokinetic model				Lower		Upper	Median	Lower		Upper
CL/F	(L/hr)	CL/F = THETA(1) * (Age/52) ** THETA(10) * (CLcr/108) ** THETA(11) * THETA(12) ** White * THETA(13) ** Gender								
THETA(1)		9.10		8.73	-	9.47	9.15	8.77	-	9.77
THETA(10)		-0.195		-0.291	-	-0.0986	-0.189	-0.256	-	-0.103
THETA(11)		0.0739		-0.0133	-	0.161	0.0781	-0.00460	-	0.165
THETA(12)		0.870		0.820	-	0.920	0.872	0.807	-	0.920
THETA(13)		0.902		0.857	-	0.947	0.895	0.856	-	0.961
Vc/F	(L)	Vc/F = THETA(2) * (Body weight/76) * THETA(7) ** non-Cancer * THETA(8) ** Cancer * THETA(9) ** Food condition								
THETA(2)		75.9		73.2	-	78.6	76.0	72.7	-	78.4
THETA(7)		1.20		1.12	-	1.28	1.19	1.11	-	1.26
THETA(8)		1.27		1.05	-	1.49	1.28	1.15	-	1.38
THETA(9)		1.12		1.05	-	1.19	1.12	1.05	-	1.22
Q/F	(L/hr)	4.77		4.16	-	5.38	4.73	4.16	-	5.29
Vp/F	(L)	41.8		38.4	-	45.2	41.6	38.5	-	44.3
Ka	(hr^{-1})	Ka = THETA(5) * (Age/52) ** THETA(14)								
THETA(5)		2.94		2.32	-	3.56	2.90	2.43	-	3.51
THETA(14)		-1.16		-1.26	-	-1.06	-1.23	-1.49	-	-1.10
ALAG	(hr)	0.195		0.188	-	0.202	0.196	0.190	-	0.198
Inter-individual variability (CV%)										
CL/F	%	37.9	6.6	35.2	-	40.5	38.6	34.9	-	41.6
Vc/F	%	25.3	40.5	20.8	-	29.2	25.2	22.4	-	28.5
Q/F	%	46.3	60.6	29.9	-	58.2	47.5	30.0	-	64.8
Vp/F	%	36.3	57.1	30.2	-	41.6	36.2	30.6	-	42.0
Ka	%	161.2	32.6	142.7	-	177.9	161.0	145.1	-	176.0
Intra-individual variability (CV%)										
proportional	%	25.7	10.8	24.5	-	26.9	25.5	24.4	-	26.7

Abbreviations: Apparent total clearance (CL/F); Apparent volume of central compartment (Vc/F); Apparent inter-compartmental clearance (Q/F); Apparent volume of peripheral compartment (Vp/F); First-order rate of absorption (Ka); Absorption lag time (ALAG).
White = 1 for non-White, White = 0 for White; Gender =1 for female, Gender = 0 for male; non-Cancer = 1 and Cancer = 0 for patients with chronic non-cancer pain and OIC, non-Cancer = 0 and Cancer = 1 for cancer patients with OIC, non-Cancer = 0 and Cancer = 0 for healthy subjects; Food = 1 for fed condition, Food = 0 for fasted condition.

Limitations were identified in the methodology used for model building. Especially, the data from OINE study should have been included in the model building data set or used to externally validate the model.

Even though it is agreed that OINE study design is not clinically relevant for healthy subjects and OIC patients, the fact that the proposed model shows good predictive performances on these data would bring additional evidence on the liability and the robustness of the model. The applicant was therefore asked to provide results of fitting performances of the proposed model on data from OINE study**.** It was noticed that, while the fitting performances were acceptable for PK concentrations after 0.1mg, the model clearly over-predicted concentrations after 1mg dose. The population model is therefore not considered to adequately describe the observed concentrations. The reason why data from the concomitant treatment period in the Phase 1 DDI studies [1202V9218, 1403V921D, and 1502V921E]) in which a P-gp/CYP3A inhibitor/inducer was co-administered with naldemedine and reason why 10 and 6 patients in phase III studies taking moderate and strong inducers were excluded was not provided. This was questioned given that inclusion of these data would permit better characterization of covariate effects of P-gp/CYP3A inhibitor/inducer on CL and F. Parameterization of the model is possible to differentiate the different

scenarios. Moreover, it is always considered better practice to use all available relevant data in model development and/or external evaluation. The applicant was therefore asked to provide results of fitting performances of the proposed model on data from Phase 1 DDI studies [Studies V9218, V921D and V921E]. However, the fitting performance for the sequences were patients were only administered naldemedine were not provided, neither were conditional weight residuals related plots.

Data provided were therefore not considered sufficient to support the adequacy of the population model to adequately the observed concentrations.

Correlated covariates such as health status and age, health status and formulation, health status and renal function (CLcr), age and strong inhibitors, Japanese and weight, CLcr and bodyweight, CLcr and age, formulation and age etc were allowed to be tested on the same covariate during the forward inclusion step and some were retained in the final model. This questions the adequacy and the validity of the proposed final model given that it cannot be excluded that the estimation of some covariate effects were confounded. It was asked that covariate analysis was redone, driven by mechanistic understanding and pharmacological or physiological rationale and that simultaneous test of correlated covariates are avoided. The applicant acknowledges the existence of correlations in covariates concomitantly used in the final model. It is argued the covariates included in the developed population PK model are physiologically reasonable. This is only partially accepted. The applicant provided the results of correlation analysis for the different correlated variables in the final model and provided evidence that these correlations are consistent with what is always expected in the target population. The results showed that some of the covariates in the final model were strongly correlated. As acknowledged by the applicant, covariates were retained in the model when they were statistically significant according to the standard procedure based on objective function in NONMEN even if they had significant correlations. This is not acceptable for a model to be considered predictive of yet unobserved data.

CLcr was retained in the final model, despite not meeting the statistical inclusion criteria, based on a strong pharmacological or physiological rationale for its inclusion. It is hardly understandable why the same approach was not applied to CYP3A inhibitors and inducers. The approach taken by the applicant is not supported. In the applicant's answer, it is acknowledged that the effect of CYP3A inducers on naldemedine pharmacokinetics could not be appropriately assessed during the population PK modelling because the number of patients with concomitant use of CYP3A inducers in Phase 2/3 studies were limited (N=16 out of 949). This is concurred. One solution to this would be to include data from DDI studies in the modelling dataset and fix parameters parameter estimates to the one estimated using non-compartmental analysis and to ensure that the model still fits the data. While it is acknowledged that PK modelling results were not used to inform labelling, the applicant was strongly advised to do this exercise. This would allow having consistent results across the different analyses.

Similarly, the fact that neither liver function enzymes nor CYP inducers/inhibitors were included in the model despite the fact that the drug is known to be mostly cleared liver metabolism through CYP decreases the liability of the proposed model. The applicant was asked to include data from DDI studies in the modelling dataset and fix parameters parameter estimates to the one estimated using non-compartmental analysis and to ensure that the model still fits the data. While it is acknowledged that PK modelling results were not used to inform labelling, the applicant is strongly advised to do this exercise. This would allow having consistent results across the different analyses. The applicant did the exercise as requested by the CHMP but was not able to provide an optimized model able to adequately fit all the available data. This shows once more that the proposed model still needs refinement before it can be consider adequate for predictive purposes.

However, as the model is currently not used for labelling and has for now quite low impact in the overall description of the drug's PK deficiencies were not further pursued in this procedure. The present model

would need further refinement if the applicant proposes to use the modelling results to support any important claim post-marketing.

Healthy subjects versus OIC patients

Pharmacokinetics in healthy subjects ([Study V921A]; Dose 0.2 mg, to-be-marketed Tablet) and OBD subjects with chronic non-cancer pain ([Study V9214]; Dose 0.1 mg and 0.3 mg, 0.1 mg tablet) were compared. Pharmacokinetics in healthy subjects and OIC subjects were also compared by population pharmacokinetic analysis. Population pharmacokinetic analysis of naldemedine indicated that health status (healthy subjects/ subjects with chronic non-cancer pain and OIC/ subjects with cancer and OIC) was a significant covariate on Vc/F; however, Vc/F of OIC subjects with chronic non-cancer and cancer pain are only 1.20- and 1.27-fold greater than that of healthy subjects and health status was not a significant covariate on CL/F.

The results suggested that no clinically meaningful difference in naldemedine pharmacokinetics were observed among healthy subjects, subjects with chronic non-cancer pain and OIC and subjects with cancer and OIC.

Special populations

No specific studies have been conducted to directly investigate the effect of age, gender, and race on naldemedine PK but effects have been estimated from the population PK analysis. Specific studies in subjects with renal impairment (Study V921B) and hepatic impairment (Study V921C) have been performed.

Impaired renal function

Study V921B, a Phase 1, multi-centre, open-label, non-randomised study was conducted to evaluate the pharmacokinetics, safety and tolerability of naldemedine in subjects with varying degrees of renal impairment and in matched control subjects with normal renal function. Pharmacokinetics of a single 0.2 mg dose of naldemedine in subjects with mild (MDRD-eGFR 60 to < 90 mL/min), moderate (MDRD-eGFR 30 to <60 mL/min), or severe renal impairment (MDRD-eGFR <30 mL/min) or ESRD requiring haemodialysis was compared with that of healthy subjects with normal renal function to demographically-matched subjects with moderate renal impairment. The effect of haemodialysis on the clearance of naldemedine was determined both before and after haemodialysis. Renal function was classified at the screening based on estimated creatinine clearance (CLcr) using Cockcroft-Gault equation for subjects with normal renal function and estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) equation for subjects with renal impairment. A single oral dose of 0.2 mg naldemedine was administered to subjects with normal renal function or mild, moderate or severe renal impairment on the morning of Day 1 in the fasted state. Subjects with ESRD requiring haemodialysis were dosed approximately 1 to 2 hours after completion of a haemodialysis session on Day 1 in the fasted state, and 2 hours prior to start of haemodialysis on Day 15 in the fasted state.

The pharmacokinetic parameters of naldemedine are summarised by renal function group in the table below. Results of ANOVA indicated that geometric mean ratios (corresponding 90% CI) of $AUC_{0\text{-inf}}$ in mild, moderate, and severe renal impairment and subjects with ESRD requiring haemodialysis compared to healthy controls were 1.0768 (0.9036 – 1.2832), 1.0603 (0.8898 – 1.2635), 1.3777 (1.1400 – 1.6650), and 0.8276 (0.6945 – 0.9862), respectively. The geometric mean values for $t_{1/2,z}$ were prolonged in subjects with severe renal impairment (18.7 hr) compared to healthy controls (13.8 hr). However, the pharmacokinetic change is small (< 1.4-fold) and no clinically meaningful differences in naldemedine pharmacokinetics were observed in subjects with mild, moderate, severe renal impairment or ESRD requiring haemodialysis compared with subjects with normal renal function. No dose adjustment for

naldemedine is necessary in subjects with mild, moderate, or severe renal impairment, or subjects with ESRD requiring dialysis.

Table 4 Summary of Naldemedine Pharmacokinetic Parameters for Various Renal Functional Groups and Statistical Analysis of Effect of Renal Impairment on the Pharmacokinetics of Naldemedine.

Parameter	Renal Functional Group	N	Geometric Mean (CV% of Geometric Mean)	Least Squares Geometric Mean Ratio (90% Confidence Interval) [b] (Renal Impairment / Healthy Subjects)
C_{max} (ng/mL)	Healthy subjects	8	3.39 (20.7)	---
	Mild	8	3.01 (23.7)	0.8872 (0.7354, 1.0704)
	Moderate	8	2.56 (25.5)	0.7546 (0.6254, 0.9103)
	Severe	6	2.76 (13.4)	0.8125 (0.6634, 0.9951)
	ESRD	8	2.81 (24.8)	0.8292 (0.6873, 1.0004)
$AUC_{0\text{-last}}$ (ng·hr/mL)	Healthy subjects	8	22.94 (18.3)	---
	Mild	8	24.62 (23.5)	1.0735 (0.9084, 1.2687)
	Moderate	8	23.81 (22.4)	1.0380 (0.8783, 1.2267)
	Severe	6	30.41 (16.1)	1.3259 (1.1071, 1.5881)
	ESRD	8	18.88 (17.3)	0.8231 (0.6965, 0.9727)
$AUC_{0\text{-inf}}$ (ng·hr/mL)	Healthy subjects	8	23.55 (18.9)	---
	Mild	8	25.35 (24.6)	1.0768 (0.9036, 1.2832)
	Moderate	8	24.97 (23.6)	1.0603 (0.8898, 1.2635)
	Severe	6	32.44 (18.1)	1.3777 (1.1400, 1.6650)
	ESRD	8	19.49 (17.9)	0.8276 (0.6945, 0.9862)
$t_{1/2,z}$ (hr)	Healthy subjects	8	13.8 (17.7)	---
	Mild	8	14.2 (25.4)	1.0330 (0.8539, 1.2497)
	Moderate	8	17.2 (23.1)	1.2474 (1.0311, 1.5090)
	Severe	6	18.7 (15.7)	1.3606 (1.1076, 1.6712)
	ESRD	8	15.2 (28.1)	1.1030 (0.9117, 1.3343)
T_{max} [a] (hr)	Healthy subjects	8	0.75 (0.50, 0.75)	
	Mild	8	0.50 (0.25, 0.75)	
	Moderate	8	0.63 (0.50, 1.50)	---
	Severe	6	0.75 (0.50. 0.75)	
	ESRD	8	0.79 (0.50, 1.00)	

a Median (Minimum, Maximum)

b The analysis is based on the analysis of variance model. Results were exponentiated to present geometric mean ratios.

Impaired hepatic function

Study V921C was a multi-centre, open-label, non-randomised study to evaluate the pharmacokinetics, safety and tolerability of naldemedine in subjects with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment and in healthy matched control subjects with normal hepatic function. Pharmacokinetics after administration of a single 0.2 mg dose of naldemedine in subjects with mild or moderate hepatic impairment was compared with that of demographically-matched healthy subjects with normal hepatic function. Healthy control subjects were matched to subjects with moderate hepatic impairment with respect to age (± 10 years), BMI (± 20%), and gender. A single oral dose of 0.2 mg naldemedine was administered to each subject in the morning on Day 1 of the study in the fasted state.

The pharmacokinetic parameters of naldemedine are summarised by hepatic function in the table below. Results of analysis of variance (ANOVA) indicated that the geometric mean values for $AUC_{0\text{-inf}}$ were not

increased in subjects with mild and moderate hepatic impairment compared with healthy subjects with normal hepatic function with geometric mean ratios (corresponding 90% confidence intervals [CI]) of 0.8284 (0.6569 - 1.0448) and 1.0516 (0.8339 - 1.3262), respectively. The geometric mean values for $t_{1/2,z}$ were not prolonged in subjects with mild and moderate hepatic impairment (mild: 14.0 hr, moderate: 13.3 hr) compared with healthy subjects with normal hepatic function (13.5 hr). Therefore, no clinically meaningful differences in naldemedine pharmacokinetics were observed between subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) and healthy subjects with normal hepatic function. No dose adjustment for naldemedine in subjects with mild or moderate hepatic impairment is necessary.

Table 5 Summary of Naldemedine Pharmacokinetic Parameters for Various Hepatic Functional Groups and Statistical Analysis of Effect of Hepatic Impairment on the Pharmacokinetics of Naldemedine.

Parameter	Hepatic Functional Group	N	Geometric Mean (CV% of Geometric Mean)	Least Squares Geometric Mean Ratio (90% Confidence Interval) [b] (Hepatic Impairment / Healthy Subjects)
C_{max} (ng/mL)	Healthy subjects	8	2.71 (26.3)	---
	Mild	8	2.44 (47.4)	0.8998 (0.6864, 1.1796)
	Moderate	8	2.93 (16.8)	1.0784 (0.8226, 1.4137)
$AUC_{0\text{-last}}$ (ng·hr/mL)	Healthy subjects	8	23.10 (22.8)	---
	Mild	8	19.10 (36.4)	0.8270 (0.6546, 1.0448)
	Moderate	8	24.18 (21.7)	1.0470 (0.8288, 1.3228)
$AUC_{0\text{-inf}}$ (ng·hr/mL)	Healthy subjects	8	23.61 (22.8)	---
	Mild	8	19.56 (35.9)	0.8284 (0.6569, 1.0448)
	Moderate	8	24.82 (21.8)	1.0516 (0.8339, 1.3262)
$t_{1/2,z}$ (hr)	Healthy subjects	8	13.5 (9.3)	---
	Mild	8	14.0 (15.1)	1.0373 (0.9042, 1.1900)
	Moderate	8	13.3 (21.5)	0.9852 (0.8588, 1.1302)
T_{max} [a] (hr)	Healthy subjects	8	0.75 (0.50, 1.00)	
	Mild	8	0.75 (0.50, 2.00)	---
	Moderate	8	0.63 (0.50, 0.75)	

a Median (Minimum, Maximum)

b The analysis is based on the analysis of variance model. Results were exponentiated to present geometric mean ratios.

The pharmacokinetics of naldemedine has not been evaluated in subjects with severe hepatic impairment (Child-Pugh Class C), therefore naldemedine should be avoided as described in section 4.4 of the SmPC.

Gender

No specific study was conducted to directly investigate the effect of gender on naldemedine pharmacokinetics. The effect of gender was evaluated in population pharmacokinetic analysis showing that gender was a significant covariate on CL/F of naldemedine. But the CL ratio of female to male was only 0.902 and the effect of gender on CL/F or AUC was small.

These results suggested that no clinically meaningful differences by gender in naldemedine pharmacokinetics were observed. No dose adjustment is required for males or females.

Race

No specific study was conducted to directly investigate the effect of race on naldemedine pharmacokinetics.

A comparison of naldemedine pharmacokinetics at doses ranging from 0.1 to 2 mg in the fasted state was conducted between Japanese healthy subjects [Single dose study V9211; Dose 0.1 and 0.3 mg, solution] and US healthy subjects [Mass balance study V9215; Dose 2 mg, solution and BA/FE study (To-be-marketed Tablet) V921A; Dose 0.2 mg, 0.2 mg tablet]. The effect of race ("White" or "non-White", "Japanese" or "non-Japanese") was also evaluated in population pharmacokinetic analysis. Population pharmacokinetic analysis of naldemedine showed that CL/F of non-White was smaller than that of White; however, CL/F ratio of non-White to White was only 0.870 and the effects of race on CL/F or AUC were small. Population pharmacokinetic analysis of naldemedine showed that there were not statistically significant pharmacokinetic differences between Japanese and non-Japanese.

No clinically meaningful differences in naldemedine pharmacokinetics were observed between White and non-White subjects and among races. Hence, no dose adjustment is required based on race.

Weight

No specific study was conducted to directly investigate the effect of body weight on naldemedine pharmacokinetics. The effect of body weight or BMI was evaluated in population pharmacokinetic analysis. Population pharmacokinetic analysis of naldemedine showed that body weight was a significant covariate on Vc/F of naldemedine.

These results suggested that there were no tendency between AUC and body weight, and between AUC and BMI. While, these results suggested there were negative correlations between C_{max} and body weight and between C_{max} and BMI, however, C_{max} ratios for all groups categorised by body weight or BMI were in the range from 0.76-fold to 1.31-fold and 0.90-fold to 1.12-fold compared to overall mean C_{max} of 2.20 and 2.65 ng/mL in subjects with chronic non-cancer pain and OIC in Phase 3 studies [Study V9231 and V9232] and subjects with cancer and OIC in Phase 3 studies [Study V9236], respectively. In conclusion, no clinically meaningful differences were observed in naldemedine pharmacokinetics by body weight and BMI. No dose adjustment is required for body weight and BMI.

Elderly

No specific study was conducted to directly investigate the effect of age on naldemedine pharmacokinetics. The effect of age was evaluated in a population pharmacokinetic analysis [Study S-297995-CB-318-N]. Population pharmacokinetic analysis of naldemedine showed that age was a significant covariate on CL/F and K_a of naldemedine. But the power coefficient for age on CL/F was only -0.195 and the effect of age on CL/F or AUC was small.

These results suggested that no clinically meaningful differences in naldemedine pharmacokinetics were observed between elderly subjects above the age of 65 years and non-elderly subjects. No dose adjustment is required for elderly subjects above the age of 65 years.

Children

The pharmacokinetics of naldemedine in paediatric subjects has not been established.

In the SmPC, the applicant mentions in Section 4.2 that for paediatric population: "The safety and efficacy of naldemedine in children and adolescents aged below 18 years have not yet been established".

Pharmacokinetic interaction studies

In vitro drug-drug interactions

Before the *in vivo* studies, the potentials of naldemedine and nor-naldemedine to inhibit or induce the metabolism of other drugs or the potentials to inhibit any of the transporters (known to be involved in clinically relevant in vivo interactions) have been investigated in the *in vitro* studies. Nor-naldemedine is

the main phase I metabolite. Because the AUC of nor-naldemedine is not both larger than one fourth of the AUC of parent drug and larger than 10% of the drug-related exposure, the determination of the inhibitory/inducer potentials on enzymes and transporters is considered not required.

Interactions related to enzyme inhibition

The *in vitro* studies conducted suggest that naldemedine at therapeutic dose is not expected to cause clinically relevant direct or time-dependent inhibition of CYP1A2, CYP1A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A and CYP4A11. The same conclusions can be drawn for nor-naldemedine, except for CYP2E1 and CYP4A11 that were not investigated. No *in vitro* or no dedicated *in vivo* studies have been performed to investigate whether naldemedine inhibits UDP-glucuronosyltransferase isoenzymes (UGTs).

Interactions related to transporters inhibition

The relative activities in the uptake transporters OCT1, OCT2, OATP1B1, OATP1B3, OAT1 and OAT3 were more than 50 % at 4.51 µM naldemedine without preincubation with naldemedine. However, the impact of a pre-incubation step on the inhibitory potential of naldemedine are recommended to be investigated post authorisation for OATP1B1, OATP1B3, OAT1 and OAT3, taking into account the actual naldemedine concentrations present in the *in vitro* system used. A low potential to cause a clinically significant BCRP inhibition has been shown.

Study R297995-PF-067-N shows that naldemedine is a very slight P-gp inhibitor at high concentrations. There were 80% efflux of digoxin remaining in presence of 3.40 µM naldemedine. The risk for drug-drug interactions through an inhibition mechanism at the level of investigated efflux transporter P-gp is unlikely at clinically relevant naldemedine concentrations.

The potential inhibitory impact of the main metabolite nor-naldemedine on transporters has also been investigated. No inhibitory effects have been shown for P-gp, BCRP. The cleared volumes of substrate in the uptake transporters OCT1, OCT2, OATP1B1, OATP1B3, OAT1 and OAT3 were more than 50 % of control at 20 nmol/L nor-naldemedine and consequently it can be concluded that the risk for drug-interactions at the investigated transporters is unlikely at clinically relevant nor-naldemedine concentrations. However, the adequacy of the length of the pre-incubation step used for OATP1B1, OATP1B3, OAT1 and OAT3 to ensure sufficient time for time-dependent inhibition to be manifested is questioned and results for P-gp should have been further confirmed in another separate system. Nevertheless, these issues were not pursued for nor-naldemedine as the determination of its inhibitory potential on transporters is considered not required.

Regarding the efflux transporters MATE1, MATE2-K and BSEP, no or only minor inhibitions have been found at 0.18 µM naldemedine or at 20 nmol/L nor-naldemedine and consequently clinically relevant inhibitions can be excluded.

Summary for inhibition of enzymes or transporters

Two tables with the relevant concentrations are proposed below by the assessor for secondary assessment:

Table 6 Table with relevant concentrations used in the assessment of in vitro enzyme/transporters inhibition by naldemedine and nor-naldemedine

		IC50 CYP3A midazolam (µM)[a]	IC50 CYP3A testosterone (µM)[a]	IC50 CYP2D6 (µM)[a]	IC50 CYP2C19 (µM)[a]	IC50 CYP2C9 (µM)[a]	IC50 CYP2C8 (µM)[a]	IC50 CYP2B6 (µM)[a]	IC50 CYP2E1 (µM)[a]	IC50 CYP4A11 (µM)[a]	IC50 CYP1A2 (µM)[a]	50 x $Cmax_{ss,u}$ (µM)*	0.1xdose/250 ml (µM)**	25 x estimated hepatic inlet $C_{max(u)}$ (µM)***
Naldemedine	Direct inhibition	>20	>20	>20	>20	>20	>20	>20	>20	>20	>20	0.02	0.14	0.07
	Time-dependant inhibition	>20	>20	>20	>20	>20	>20	>20	>20	>20	>20			
Nor-naldemedine	Direct inhibition	>20	>20	>20	>20	>20	>20	>20	N.D	N.D	>20	0.015	N.A	
	Time-dependant inhibition	>20	>20	>20	>20	>20	>20	>20	N.D	N.D	>20			

[a]studies R-297995-PF-064-N and S-297995-PB-338-N

naldemedine molecular weight: 570.65g/mol (free base)

*C_{max} = 3.39ng/mL = 0.00594 µM (study V921B after a single dose of naldemedine 0.2 mg in healthy volunteers), protein binding = 6.8% → $C_{max,unbound}$ = 0.00594 x 0.068 ➔ 50 x 0.0004 = 0.02 µM

**0.1 x 0.2 mg/0.25 = 0.08mg/L = 0.14 µM

*** 25 x estimated hepatic inlet $C_{max(u)}$ = 25 x ($f_{unbound,plasma}$/Rb) x (C_{max} x Rb + (F_a x F_g x k_a x dose/Q_H)) = 0.07 µM with $I_{max,b}$ = 0.00594 µM, $F_{unbound,plasma}$ = 0.068, F_a = 1 (worst case), F_g = 1 (worst case), k_a = 0.1/min (worst case), Q_H = 97 L/h = 1.62 L/min, Rb = Blood/Plasma ratio = 0.632, dose = 0.35 µM (0.2 mg).

N.A: not applicable; N.D: not determined

Table 7 Inhibitory effect of naldemedine and nor-naldemedine on transporters (% of control)

Transporter	**Naldemedine****	**Nor-naldemedine at 20 nmol/L**
IC50 OAT1 (µM)[a,d]	88.9 % relative activity* at 4.51 µM	93.5 % of cleared volume of substrate
IC50 OAT3 (µM)[a,d]	58.9 % relative activity* at 4.51 µM 91.6 % relative activity* at 0.9 µM	108.2 % of cleared volume of substrate
IC50 OCT1 (µM)[a,d]	97.5 % relative activity* at 4.51 µM	62.4 % of cleared volume of substrate

IC50 OCT2 (µM)[a,d]	70.5 % relative activity* at 4.51 µM 82.3 % relative activity* at 0.9 µM	101.6 % of cleared volume of substrate
IC50 OATP1B1 (µM)[a,d]	89.5 % relative activity* at 4.51 µM	93.5 % of cleared volume of substrate
IC50 OATP1B3 (µM)[a,d]	86.6 % relative activity* at 4.51 µM	94.2 % of cleared volume of substrate
IC50 BCRP (µM)[a,d]	95.38 % remaining efflux at 3.40 µM	100.5 % remaining efflux
IC50 P-gp (µM)[b,d]	79.8 % remaining efflux at 3.40 µM	99.5 % remaining efflux
IC50 MATE1 (µM)[c]	IC50 > 0.180 µM	IC50 > 20 nmol/L
IC50 MATE2-K (µM)[c]	IC50 > 0.180 µM	IC50 > 20 nmol/L
IC50 BSEP (µM)[c]	IC50 > 0.169 µM	IC50 > 20 nmol/L

[a]study S-297995-PF-297-N, [b]study R-297995-PF-067-N, [c]study S-297995-PF-344-N, [d]study S-297995-PF-340-N

*relative activity in the uptake transporter inhibition

** The actual concentrations of naldemedine in the *in vitro* inhibitor assessment for P-gp, MATE1/2-K, and BSEP were calculated using the adhesion ratios to experimental devices. The adhesion ratios measured in the inhibition studies for P-gp and MATE1/2-K were used in the calculation of actual concentrations for efflux transporter (BCRP) and uptake transporters (OATP1B1, OATP1B3, OCT1, OCT2, OAT1, and OAT3), respectively

Interactions related to enzyme/transporter induction

The *in vitro* studies S-297995-PF-176-N, S-297995-PF-298-N, S-297995-PF-347-N aimed to investigate induction potential of naldemedine and nor-naldemedine on CYP1A2, CYP2B6, CYP3A4/5 and UGT1A2, UGT1A6 and UGT2B7.

Naldemedine and nor-naldemedine have little or no inductive effect on CYP1A2 mRNA levels at clinically relevant maximal plasma concentrations and maximal intestinal concentrations.

As regard CYP2B6, the results for induction of naldemedine or nor-naldemedine can be considered as negatives.

Increasing CYP3A4 mRNA levels (> 2 fold changes) with increasing concentrations of naldemedine were observed in all donors, as well as concentration-dependent increases in CYP3A4/5 activity. Based on the basic method, a clinically significant CYP3A4 inducer potential cannot be excluded. The applicant has therefore further assessed the clinical CYP3A4 induction potential by calculating the AUC ratio (AUCR) of midazolam by both the mechanistic static model equation and the RIS correlation method. The estimated AUCR using the mechanistic static model were included in the interval 0.8-1.25. No *in vivo* studies are therefore indicated to further assess the CYP3A4 inducer potential. Using the RIS correlation method with the data from two donors on three (RIS correlation data not available for 1 donor), the same trend than those reported with the mechanistic static model with AUCR > 0.8 was observed. Since clinically significant CYP3A4 induction is not expected based on the conclusions from the mechanistic static model and the RIS correlation method, clinically relevant induction of CYP3A5, CYP2C and transporters induced through mechanisms similar than those for CYP3A4 can be considered unlikely at the intended clinical dose (0.2 mg/day).

Negative results were observed for CYP3A4 induction when the human hepatocytes were treated with nor-naldemedine.

Because clinically significant induction mediated via PXR/CAR and Ah-receptor is not expected *in vivo* since the likelihood of a significant CYP1A2, CYP2B6 and CYP3A4 induction effect of naldemedine has been excluded based on *in vitro* experiments (S-297995-PF-176-N, S-297995-PF-298-N and S-297995-PF-347-N studies), no further investigation of the inducer potential of naldemedine for UGT enzymes is needed.

In Silico

Physiologically based pharmacokinetic modelling and simulation study was performed to evaluate the effect of repeated administration of moderate CYP3A inducer efavirenz on the pharmacokinetics of naldemedine in healthy adult subjects compared to naldemedine alone.

Simulation of drug-drug interaction was performed for 140 subjects (10 trials, 14 subjects/trial) under the situation that efavirenz 400 mg was administered once daily on Day 1 to 17 and naldemedine 0.2 mg was co-administered with efavirenz as CYP3A inducer on Day 15.

PK results of 0.2 mg naldemedine administered alone from 3 phase 1 studies (V921D, V921A and S-297995-CB-330-N) and DDI study results co-administered with cyclosporine and fluconazole from 2 phase 1 studies (V9218 and V921E) were used for model building. The contribution of drug metabolism via CYP3A4 was included in the naldemedine PBPK model, and the contribution of drug metabolism via UGT1A3 and the transport via P-gp were not included to predict in vivo DDI potency of naldemedine with efavirenz, which is not considered to have influence on UGT1A3 and P-gp.

Co-administration of naldemedine with multiple dose of efavirenz for 15 days demonstrated lower naldemedine concentration compared with a single dose of naldemedine. The ratios of geometric mean naldemedine Cmax and AUC values following co-administration of efavirenz with naldemedine compared with naldemedine alone were 0.59 (range: 0.55 to 0.64) and 0.52 (range: 0.47 to 0.55), respectively, from the simulation of 10 trials.

In conclusion, simulation using PBPK modelling suggested that concomitant use of the moderate CYP3A inducer efavirenz 400 mg once daily for 15 days decreased the AUC of naldemedine by 48%. This decrease is considered not to be clinically meaningful. However, given the remaining uncertainty in the model and given that SIMCYP plateform is currently not considered qualified for to characterize drug induction (in the absence of in vivo data), the effect of moderate inducers (e.g. efavirenz,) can therefore not be established; therefore, the use of rizmoic acid should cautiously be considered in patients already given a moderate inducer (see SmPC sections 4.4 and 4.5).

In vivo drug-drug interaction studies

Based on *in vitro* metabolism and transporter data, in vivo drug-drug interactions of naldemedine were designed to assess effects of P-gp inhibition, CYP3A induction and inhibition on naldemedine as a substrate.

The effects of co-administered drugs on the pharmacokinetics of naldemedine are summarised in the figure below:

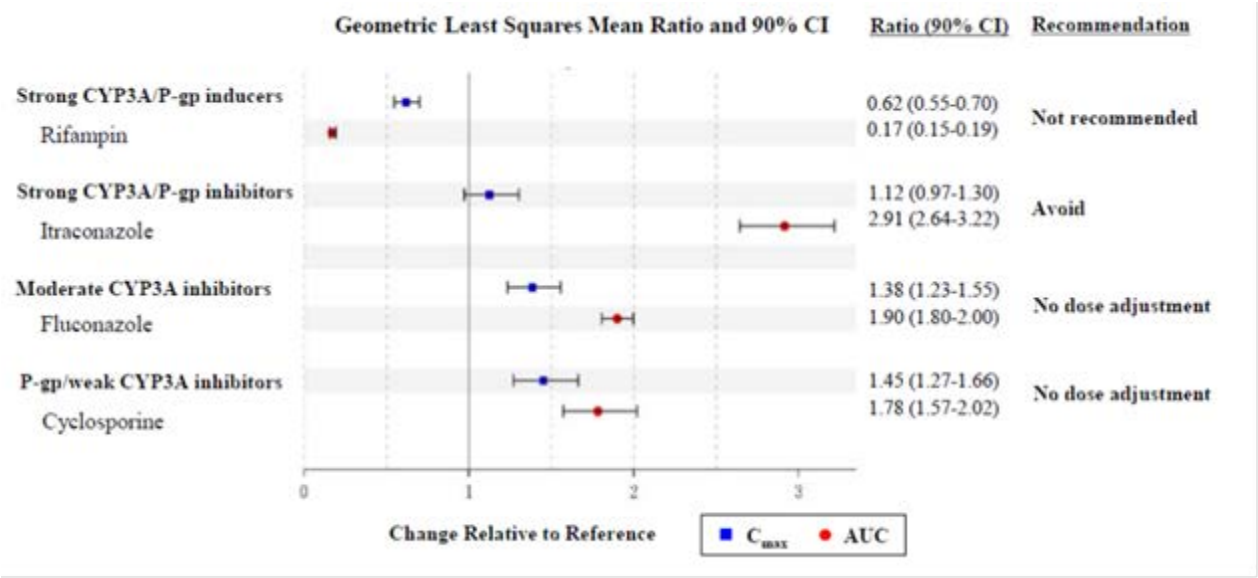


Figure 3 Summary of the Effect of Co-administered Drugs on the Pharmacokinetics of Naldemedine

It is not judged necessary to further investigate the metabolites' exposures in the *in vivo* interaction studies since systemic exposures of nor-naldemedine and naldemedine 3-G were only 9% to 13% and 1% to 2%, respectively, of that of naldemedine. Radioactivity accounted for less than 10% of total radioactivity exposure across the studies using both labelled compounds. In addition, no antagonistic or agonistic activities are expected to be associated to nor-naldemedine at the recommended clinical dose (see non clinical aspects). No adverse effects have been observed in the non-clinical safety pharmacology section for any metabolites.

Study 1502V921E with itraconazole/fluconazole

The study is an open-label, one-sequence, two-period, crossover, drug-drug interaction study to evaluate the effect of repeated administration of itraconazole and fluconazole on the pharmacokinetics of naldemedine in Japanese healthy adult subjects.

Test product: Naldemedine, 0.2-mg tablet for oral administration. Each subject in Cohort 1 (itraconazole) and Cohort 2 (fluconazole) received a single 0.2 mg dose of naldemedine in the fasted state on Days 1 and 9 of the study. Batch n° CF5005.

Reference products: Itrizole® Oral Solution 1%, Fluconazole 100-mg capsule.

A single-dose of naldemedine as victim is appropriate as it has linear pharmacokinetics and the dose used (0.2mg) is included in the linear range (0.1-100mg). The systemic exposure of the perpetrators are adequate as obtained with sufficient high doses under therapeutic (steady state) conditions (400 mg on day 5 and 200 mg once daily on Day 6 to 11 for itraconazole and fluconazole).

Table 8 Summary of Plasma Naldemedine Pharmacokinetic Parameters and Statistical Comparisons Following Administration of Naldemedine Alone and Naldemedine plus Itraconazole (PK Parameter Population)

Parameters	Plasma Naldemedine		
	Geometric Mean (CV% Geometric Mean)		Naldemedine plus Itraconazole / Naldemedine Alone Geometric Least Squares Mean Ratio[a] (90% CI: lower, upper)
	Naldemedine Alone	Naldemedine plus Itraconazole	
C_{max} (ng/mL)	3.56 (38.2)	4.00 (20.2)	1.1237 (0.9706, 1.3010)
$AUC_{0\text{-}last}$ (ng·hr/mL)	26.73 (38.2)	70.88 (34.4)	2.6517 (2.3968, 2.9338)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	26.98 (37.7)	78.64 (35.3)	2.9149 (2.6420, 3.2160)
λ_z (1/hr)	0.0665 (24.8)	0.0313 (17.8)	0.4698 (0.4291, 0.5143)
$t_{1/2,z}$ (hr)	10.4 (24.8)	22.2 (17.8)	2.1286 (1.9444, 2.3302)
CL/F (L/hr)	7.41 (37.7)	2.54 (35.3)	0.3431 (0.3109, 0.3785)

N = 14. CI, confidence interval.

[a] The analyses were based on the analysis of variance model.

The study indicates that naldemedine exposure increases to a moderate extent (> 2-fold and < 5-fold increase) following co-administration of a strong CYPA3A4/P-gp inhibitor: itraconazole increased Cmax, AUC0-last, and AUC0-inf of naldemedine by 1.12 fold, 2.65 fold, and 2.91 fold. The clinically meaningful effect on naldemedine exposure by itraconazole have been reported in sections 4.4 and 4.5 of the SmPC.

The systemic exposure of the perpetrator fluconazole is considered appropriate for moderate CYP3A inhibitory potential:

Table 9 Summary of Plasma Naldemedine Pharmacokinetic Parameters and Statistical Comparisons Following Administration of Naldemedine Alone and Naldemedine plus Fluconazole (PK Parameter Population)

Parameters	Plasma Naldemedine		
	Geometric Mean (CV% Geometric Mean)		Naldemedine plus Fluconazole / Naldemedine Alone Geometric Least Squares Mean Ratio[a] (90% CI: lower, upper)
	Naldemedine Alone	Naldemedine plus Fluconazole	
C_{max} (ng/mL)	3.48 (23.7)	4.81 (16.1)	1.3831 (1.2316, 1.5532)
$AUC_{0\text{-}last}$ (ng·hr/mL)	26.93 (16.5)	50.58 (13.3)	1.8782 (1.7827, 1.9789)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	27.18 (16.5)	51.60 (13.5)	1.8987 (1.8049, 1.9973)
λ_z (1/hr)	0.0683 (24.2)	0.0497 (13.1)	0.7267 (0.6670, 0.7917)
$t_{1/2,z}$ (hr)	10.1 (24.2)	14.0 (13.1)	1.3761 (1.2630, 1.4992)
CL/F (L/hr)	7.36 (16.5)	3.88 (13.5)	0.5267 (0.5007, 0.5541)

N = 14. CI, confidence interval.

[a] The analyses were based on the analysis of variance model.

Fluconazole increased Cmax, AUC0-last, and AUC0-inf of naldemedine by 1.38 fold, 1.88 fold, and 1.90 fold. These results can be categorised as a mild inhibition as it concerns an increase located in the interval of 1.25 to 2-fold increase in plasma AUC. Even if it concerns a mild inhibition, caution should be exercised as the number of TEAE increased when naldemedine is administered concomitantly with moderate CYP3A inhibitors in the clinical studies. Therefore it is mentioned in section 4.5 that concomitant administration of moderate CYP3A inhibitors such as fluconazole may increase plasma concentrations of naldemedine and patients should be monitored for safety.

The clinically meaningful effects on naldemedine exposure by itraconazole have been reported in the section 4.5 of the SPC. Some examples of well-known strong CYP3A inhibitors are provided in section 4.5. It is correctly mentioned that there is no risk of interaction with concomitant use of mild CYP3A inhibitors.

Study 1403V921D with rifampin

This study is an open-label, one-sequence, two-period, crossover, drug-drug interaction study to evaluate the effect of repeated administration of rifampin 600 mg on the PK of naldemedine in healthy adult subjects compared with naldemedine alone.

Test product: Naldemedine, 0.2 mg tablet for oral administration. Batch n° 3965864.

Reference product: Rifampin capsules USP, 300 mg. Batch n° 2013272245.

Table 10 Summary of the Statistical Comparisons of Plasma Naldemedine Pharmacokinetic Parameters: Naldemedine:Rifampin Versus Naldemedine Alone (PK Parameter Population)

Parameter	Geometric Mean (CV% of Geometric Mean)				Least Squares Geometric Mean Ratio (90% Confidence Interval) [b] (Naldemedine + Rifampin/ Naldemedine Alone)
	N	Naldemedine + Rifampin	N	Naldemedine Alone	
C_{max} (ng/mL)	14	1.68 (21.1)	14	2.72 (25.7)	0.6180 (0.5466, 0.6987)
$AUC_{0\text{-last}}$ (ng·hr/mL)	14	3.549 (16.6)	14	21.49 (19.1)	0.1651 (0.1469, 0.1856)
$AUC_{0\text{-inf}}$ (ng·hr/mL)	14	3.701 (16.0)	14	21.77 (19.2)	0.1700 (0.1512, 0.1911)
$t_{1/2,z}$ (hr)	14	3.22 (15.5)	14	11.7 (18.5)	0.2745 (0.2524, 0.2986)
T_{max} [a] (hr)	14	0.51 (0.50, 1.00)	14	1.00 (0.50, 2.50)	---

a Median (Minimum, Maximum)

b The analysis is based on the analysis of variance model. Results were exponentiated to present geometric mean ratios.

Source: Study V921D, Table 11-2, 11-3

The geometric LS mean naldemedine Cmax, AUC0-last, AUC0-inf, and t1/2,z values were approximately 38%, 83%, 83%, and 73% lower, respectively, following Naldemedine:Rifampin compared with Naldemedine Alone, and the 90% CIs for the ratios of these parameters were completely outside the 0.80 to 1.25 reference interval usually applied to establish similarity between treatments. The geometric LS mean naldemedine CL/F value was approximately 6-fold following Naldemedine:Rifampin compared with Naldemedine Alone, and the 90% CI for the ratio of CL/F was completely outside the 0.80 to 1.25 reference interval.

A single-dose study is appropriate as naldemedine (victim) has linear pharmacokinetics and the dose used (0.2mg) is included in the linear range (0.1-100mg). The systemic exposure of the perpetrator is adequate as obtained with the highest recommended doses under therapeutic (steady state) conditions (17 consecutive days of 600 mg rifampin once daily QD).

The clinically meaningful effects on naldemedine exposure by rifampin have been adequately reported in sections 4.4 & 4.5 of the SmPC.

Study 1202V9218 with cyclosporine

The study is a Phase 1, open-label, randomized, 2-way crossover study to evaluate the drug-drug interaction of the P-gp inhibitor cyclosporine with the pharmacokinetics of S-297995 in healthy adult subjects. Subjects orally received naldemedine 0.4 mg alone and naldemedine co-administered with cyclosporine 600 mg solution in the fasted state.

Table 11 Summary of Naldemedine Pharmacokinetic Parameters and Statistical Analysis of Effect of Cyclosporine on the Pharmacokinetics of Naldemedine

Parameter	Geometric Mean (CV% of Geometric Mean)				Least Squares Geometric Mean Ratio (90% Confidence Interval) [b] (Naldemedine + Cyclosporine / Naldemedine Alone)
	N	Naldemedine + Cyclosporine	N	Naldemedine Alone	
C_{max} (ng/mL)	13	7.03 (25.0)	13	4.86 (14.5)	1.4496 (1.2676, 1.6578)
$AUC_{0\text{-last}}$ (ng·hr/mL)	13	69.17 (19.2)	13	38.60 (17.2)	1.7875 (1.5746, 2.0293)
$AUC_{0\text{-inf}}$ (ng·hr/mL)	13	69.55 (19.2)	13	38.94 (17.3)	1.7811 (1.5686, 2.0223)
$t_{1/2,z}$ (hr)	13	8.89 (13.4)	13	10.6 (12.6)	0.8241 (0.7683, 0.8840)
T_{max} [a] (hr)	13	1.00 (0.50, 5.00)	13	0.75 (0.50, 1.00)	---

a Median (Minimum, Maximum)

b The analysis is based on the analysis of variance model. Results were exponentiated to present geometric mean ratios.

Source: Study V9218, Table 11-2

Naldemedine has been shown to be a P-gp substrate *in vitro*, which is further substantiated by preclinical models showing limited transfer across the blood-brain barrier. Cyclosporine is recommended as a clinical probe for Pg-P inhibition in accordance with the International Transporter Consortium (ITC, Giacomini et al. 2010) and the assessor is of the opinion that a single dose of 600 mg would provide sufficiently high plasma cyclosporine concentrations to study the effects of P-glycoprotein inhibition on naldemedine PK. The study with cyclosporine in healthy volunteers indicates that naldemedine exposure increases to a mild extent following co-administration of a P-gp inhibitor: cyclosporine increased the AUC and Cmax of naldemedine after single-dose administration by 79% and 45% respectively (< 2-fold but 90% CI AUC: 1.57-2.02). There were also increases in the Cmax, AUC0-last, for naldemedine metabolites, nor-naldemedine and naldemedine 3-G, in the presence of cyclosporine.

Naldemedine is expected to be soluble in gastrointestinal fluid independently of pH. Hence, the potential for drug interaction with gastric acid reducing agents (e.g., proton-pump inhibitors, Histamine 2 [H2]-blockers and antacids) is considered to be low. No drug interaction studies have been conducted for naldemedine with gastric acid-reducing agents. This justification for not submitting a DDI study with gastric acid reducing agents was accepted by the CHMP.

The naldemedine program performed a comprehensive assessment based on *in vitro* inhibition and induction data to evaluate potential interactions that may affect the efficacy of oral contraceptives or result in significant DDIs. The assessment included a careful evaluation of the metabolic inhibition properties of naldemedine and the potential for induction of CYP and UGT enzymes, which are responsible for the metabolism of most estrogen and progestin components of oral contraceptive agents. From the results of the assessment, naldemedine is considered unlikely to affect the efficacy of these medicinal products.

2.4.3. Pharmacodynamics

Mechanism of action

Naldemedine acts as an antagonist of μ-, δ-, and κ-opioid receptors, and has no agonistic activity at any of these opioid receptors. Naldemedine functions as a μ-opioid receptor antagonist in peripheral tissues, in particular the enteric nervous system in the gastrointestinal tract, thereby decreasing the constipating effects of opioids without reversing centrally-mediated opioid effects.

Primary and Secondary pharmacology

The analysis populations of the PK/Efficacy analysis and the PK/Safety analysis were described. The individual PK parameters (AUC) of naldemedine were used for PK/PD analysis. AUC of the subjects in the placebo group were treated as zero (0).

PK / Efficacy

Linear and Emax models were used to describe the change in SBM frequency. The linear model adequately described the relationship between the change in SBM frequency and predicted naldemedine AUC. Although the estimate of the slope for Study No. 1107V9221 was small (0.0169) relative to the other studies and its lower limit of 95% confidence interval was slightly lower than 0 (-0.0153), the other studies showed clear positive correlation between the change in SBM frequency and naldemedine AUC.

For the Emax model, the 95% confidence interval of EC50 included zero (0), suggesting the estimates of EC50 would not be reliable.

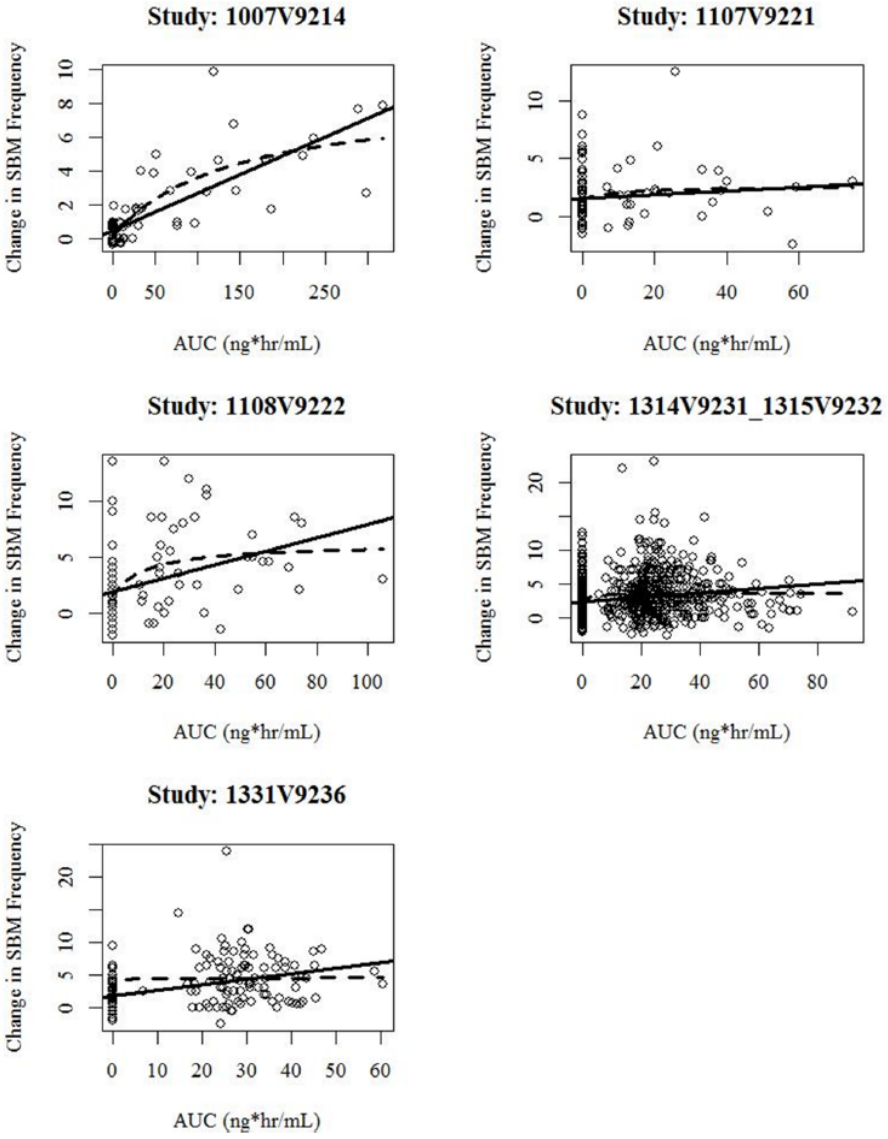


Figure 4 Plots of Linear or Emax Model Regression for Change in Spontaneous Bowel Movement (SBM) Frequency

The logistic model was used for the PK/Efficacy analysis of the SBM responder. and the parameter estimates are shown in Table below.

Table 12 Paremeter Estimates of PK/Efficacy Analysis for Spontaneous Bowel Movement (SBM) Responder

Study No.	Parameter	Estimate	95% Confidence Interval	
			Lower	Upper
1107V9221	a	-0.314	-0.797	0.159
	b	0.0191	-0.00801	0.0497
1108V9222	a	-0.502	-1.03	0.00224
	b	0.0500	0.0234	0.0839
1314V9231_1315V9232	a	-0.537	-0.700	-0.375
	b	0.0194	0.0114	0.0274
1331V9236	a	-0.554	-0.965	-0.157
	b	0.0462	0.0271	0.0664

Probability (SBM Responder) = 1 / [1 + exp (- a - b × AUC)]

The predictions from the logistic model were presented in Figure below.

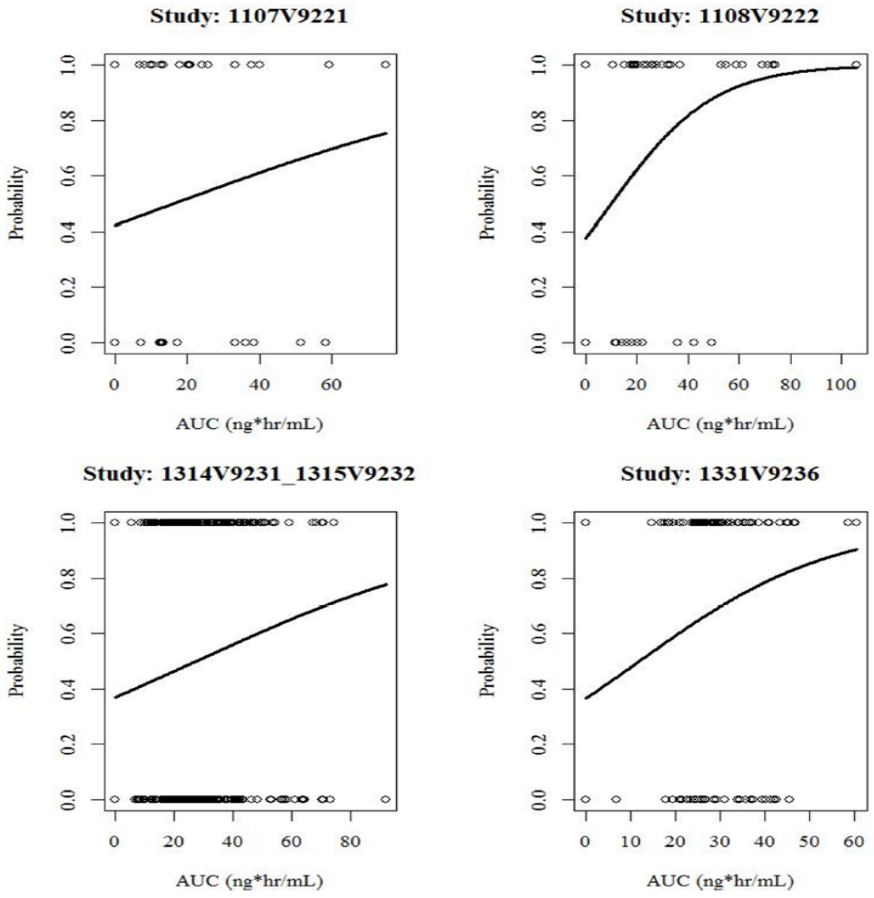


Figure 5 Plots of Logistic Regression for Spontaneous Bowel Movement (SBM) Responder

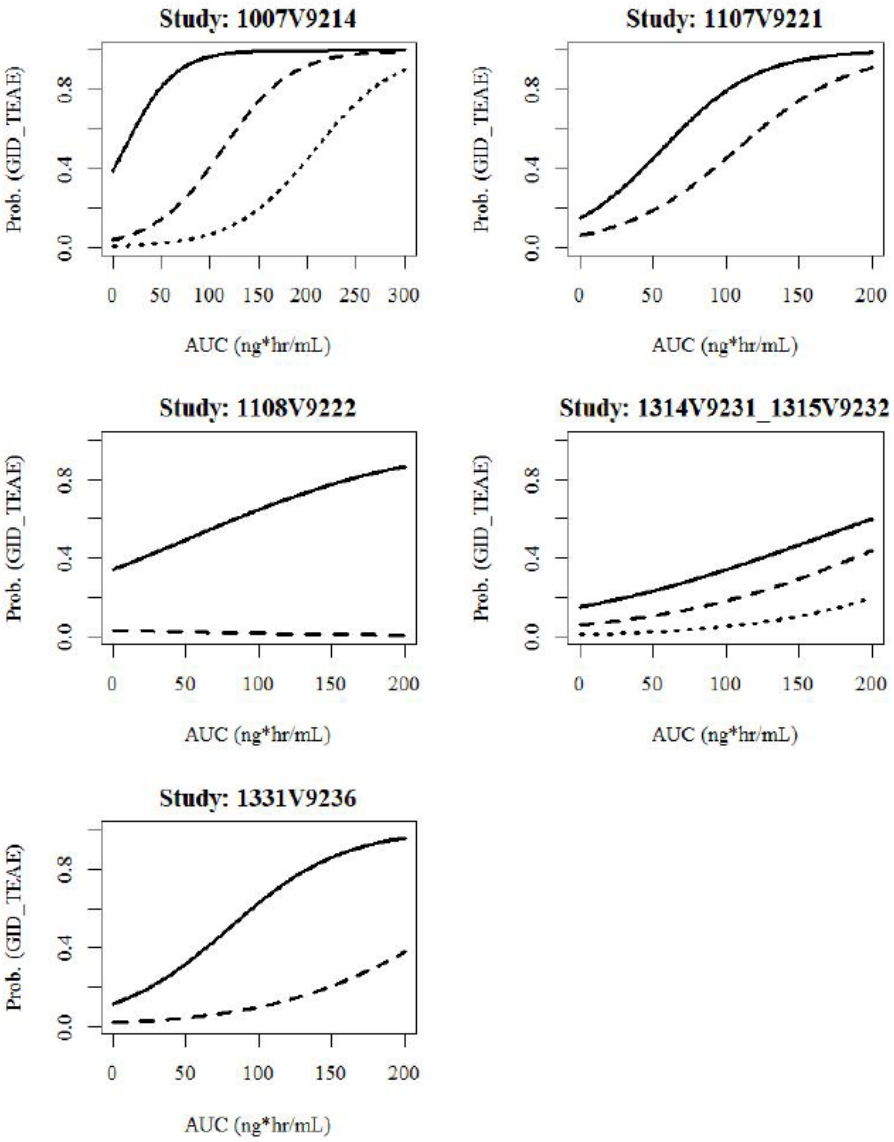
The slopes of AUC were similar across all studies and the model well described the observations. The probabilities of the SBM responder were calculated based on the developed logistic model by using the mean AUC in Table 8 of the summary of clinical pharmacology studies, and relationships between the probabilities of the SBM responder and AUC around clinical doses (placebo, 0.1, 0.2, and 0.4 mg) were summarized in Table 14 of the summary of clinical pharmacology studies. When subjects took 0.2 mg of

naldemedine in the Phase 2 and Phase 3 studies, the probabilities of the number of SBM responders were predicted to be 52.7% (patients with chronic non-cancer pain and OIC in the Phase 2b study; 1107V9221), 72.1% (cancer patients with OIC in Phase 2b study; 1108V9222), 49.9% (patients with chronic non-cancer pain and OIC in Phase 3 studies; 1314V9231 and 1315V9232), and 69.7% (cancer patients with OIC in Phase 3 study; 1331V9236).

PK / Safety

The relationship between the occurrence of TEAEs and naldemedine AUC was analysed with the logistic model. The probability of the occurrence of gastrointestinal, abdominal pain and diarrhoea TEAE increased as the AUC increased. The probabilities of the occurrence of any severe gastrointestinal disorders, abdominal pain, and diarrhea at naldemedine dose of 0.2 mg and 0.4 mg were predicted to be less than 3% in patients with chronic non-cancer pain and OIC. In cancer patients with OIC, the probabilities of the occurrence of any severe gastrointestinal disorders, abdominal pain, and diarrhoea at naldemedine dose of 0.2 mg and 0.4 mg were not estimated because of few number of severe TEAEs reported in these studies.

The relationship between the occurrence of treatment related AE and predicted naldemedine AUC was analyzed with the logistic model. The results were similar to those of TEAE.



Logistic model was used for PK/PD analyses with severity and the estimated probabilities were indicated (solid curve: probability of mild, moderate, or severe AE, long dotted curve: probability of moderate or severe AE, dotted curve: probability of severe AE).

Figure 6 Probability of AE of Gastrointestinal Disorders vs AUC in Phase 2 and Phase 3 Studies (subjects with chronic non-cancer pain and OIC: Study V9214, V9221, V9231 and V9232; subjects with cancer and OIC: V9222 and V9236)

The probability of the occurrence of any severe gastrointestinal disorders, abdominal pain and diarrhoea at naldemedine dose of 0.2 mg and 0.4 mg were predicted as less than 3% in subjects with chronic non-cancer pain and OIC. In subjects with cancer and OIC, the probability of the occurrence of any severe gastrointestinal disorders, abdominal pain and diarrhoea at naldemedine dose of 0.2 mg and 0.4 mg were not estimated because of little severe TEAE reported.

Table 13 Summary of Gastrointestinal Disorders (Adverse Events) and AUC in Phase 2 and Phase 3 Studies (subjects with chronic non-cancer pain and OIC: Study V9214, V9221, V9231 and V9232; subjects with cancer and OIC: V9222 and V9236)

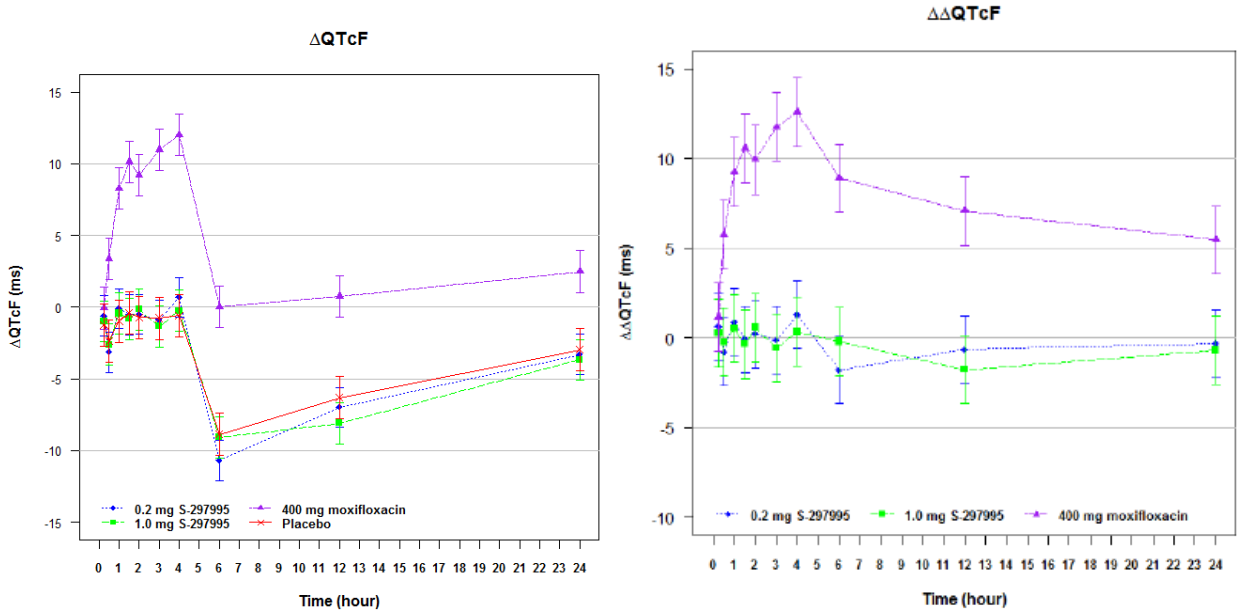
Study	Phase	Dose (mg)	N	Number of AE Occurred Mild/Moderate/Severe (% AE, % Severe AE Occurred)	Mean of $AUC_{0\text{-}inf}$ or $AUC_{0\text{-}\tau}$ at Steady State (ng·hr/mL)
V9214	2	0	18	7 / 0 / 0 (38.9%, 0%)	0
		0.01	9	5 / 0 / 0 (55.6%, 0%)	0.8733
		0.03	9	3 / 0 / 0 (33.3%, 0%)	2.375
		0.1	9	1 / 0 / 0 (11.1%, 0%)	11.43
		0.3	9	6 / 3 / 0 (100.0%, 0%)	30.74
		1	9	5 / 3 / 0 (88.9%, 0%)	92.84
		3	9	1 / 2 / 6 (100.0%, 66.7%)	222.3
V9221	2b	0	61	6 / 2 / 0 (13.1%, 0%)	0
		0.1	9	1 / 1 / 0 (22.2%, 0%)	10.50
		0.2	9	1 / 3 / 0 (44.4%, 0%)	22.11
		0.4	10	2 / 1 / 0 (30.0%, 0%)	43.76
V9222	2b	0	56	16 / 1 / 0 (30.4%, 0%)	0
		0.1	10	4 / 1 / 0 (50.0%, 0%)	15.66
		0.2	16	7 / 1 / 0 (50.0%, 0%)	29.07
		0.4	12	6 / 0 / 0 (50.0%, 0%)	61.09
V9231 & V9232	3	0	548	47 / 21 / 7 (13.7%, 1.3%)	0
		0.2	445	52 / 34 / 8 (21.1%, 1.8%)	27.50
V9236	3	0	96	7 / 2 / 0 (9.4%, 0%)	0
		0.2	97	20 / 1 / 2 (23.7%, 2.1%)	30.07

Pharmacokinetic comparability bounds representing clinically meaningful treatment differences for naldemedine can be based on a 90% CI of (0.50, 2.00) for the geometric mean ratio (GMR) for the exposure to naldemedine. These pharmacokinetic comparability bounds are used throughout the naldemedine programme to identify clinically meaningful differences for influencing factors, such as demographic parameters, renal and hepatic impairment and drug-drug interactions on the pharmacokinetics of naldemedine.

QTc prolongation

Study V9219 was a double blind (in regard to naldemedine and placebo), randomised, placebo- and positive-controlled, 4-period crossover study in healthy male and female subjects using single therapeutic (0.2 mg) and supratherapeutic (1 mg) doses of naldemedine, placebo, and moxifloxacin (400 mg) as positive control in separate treatment periods.

Fifty-six subjects were randomised and 44 subjects completed the study, 55 subjects were included for QT/QTc evaluation and 53 subjects were included for pharmacokinetic evaluation. The principal results are illustrated below with the figure to the right representing baseline adjusted QTcF changes:



The change of QTcF from baseline (ΔQTcF) following 0.2 mg and 1 mg dose of naldemedine were similar to placebo. As anticipated there was a clear QTcF prolongation observed after administration of a 400 mg dose of the positive control, moxifloxacin.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics:

Analytical methods

The bioanalytical methods are well described and are in accordance with the current guidelines. These bioanalytical methods are correctly validated at various analytical laboratories The characteristics of linearity, within- and between-run accuracy and precision, recovery, selectivity, sensitivity, dilution integrity, matrix effect, hemolysis effect, re-injection reproducibility and stability are within the acceptance specifications if applicable.

The applicant confirms the absence of ISR in several PK analytical studies (Reports 297995-CF-127-C, S-297995-CF-152-C and S-297995-CF-178-C). Since the studies were conducted from 2009 to 2010, the lack of ISR in these studies appears justified. In addition, the applicant states that other ISR data were obtained in the same laboratory. Indeed, for further PK analytical studies [Reports S-297995-CF-326-N, S- 297995-CF-328-N, S-297995-CF-327-N, S-297995-CF-217-N, and S-297995-CF- 252-N], the repeat analysis of the incurred samples reanalyses was performed and their results met acceptance criteria (at least 67% of the reanalysis concentrations is within ±20% of their mean of original and repeat concentrations).

ADME

The general PK characteristics (ADME) of naldemedine were adequately characterised. Similar oral bioavailability among the various formulations used in the naldemedine clinical development programme was shown. Food had no clinically significant effect on naldemedine exposure. Consistent results were obtained across studies, demonstrating rapid absorption of naldemedine and nor-naldemedine being the

main metabolite in plasma (contributing to <10% of total plasma radioactivity). Approximately 20% of the dose was excreted in urine as unchanged naldemedine. Based on the results of the mass balance study and in vitro experiments, the biotransformation pathway of naldemedine was adequately characterised. Naldemedine showed dose-proportional PK and a slight accumulation upon multiple administration, which is described in the SmPC.

Dose-proportionality with respect to Cmax and AUC following single-dose administration has been reasonably well demonstrated for a wide range of doses including those relevant to the suggested posology. Multiple dose administration has been performed with doses of 3, 10 and 30 mg daily. There appear to be a reasonable lack of time dependency with accumulation ratios for AUC and Cmax between 20 and 30%. A formal statistical analysis for time-dependency is presented from multiple-dose (3, 10 and 30 mg) study V9213. In this analysis, a slight 8% (90% CI 1-15%) increase in AUC exposure for the 3 mg dose following ten days of treatment was noted. An 8% increase in AUC following ten days of treatment with 3 mg daily is judged to be without clinical relevance.

Special populations

According to the results of the specific study (Study V921B), and of the POP PK analysis, a dose of 0.2 mg for subjects with mild, moderate, or severe renal impairment, or ESRD requiring haemodialysis is considered appropriate to ensure patient safety, and provide adequate exposure given the efficacy of 0.2 mg observed in clinical studies.

No dose adjustment is required in subjects with any degree of renal impairment.

Based on review of data from the formal hepatic impairment study and review of the POP PK analysis report, it is agreed that moderate hepatic dysfunction did not significantly affect naldemedine pharmacokinetics.

No dose adjustment is necessary for patients with mild or moderate hepatic impairment. Use in patients with severe hepatic impairment is adequately not recommended since effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of naldemedine was not evaluated.

The conclusion that naldemedine daily dosage will not have to be adjusted for gender, body weight and race factors is deemed appropriate based on the available data and accompanying POP PK analysis. It is confirmed that the differences in naldemedine exposure with body weight are not considered as clinically meaningfuland it has been included in Section 5.2 that the effect of weight on naldemedine exposure is not clinically relevant.

No dose adjustment is recommended for older people.

Naldemedine must not be used in children because no data in paediatric subjects is available.

Pharmacokinetics in target population

Population pharmacokinetic analyses

Limitations were identified in the methodology used for the pk model. However, as the model has for now quite low impact in the overall description of the drug's PK, it's deficiencies were not further pursued in this procedure. It is noted that the present PK model approach would need further refinement if the applicant proposes to use the modelling results to support any claims post-marketing.

Healthy subjects versus OIC patients

Based on the pK results collected in the studies, it can be assumed that the pharmacokinetic profiles in healthy subjects and OIC patients were similar.

Interactions

In vitro DDI

In vitro DDI studies have shown that naldemedine and nor-naldemedine did not expect to cause clinically relevant direct or time-dependent inhibition of CYP1A2, CYP1A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A or induction of CYP1A2, CYP3A4 and CYP2B6 at clinically relevant concentrations. The same conclusion can be drawn for the inhibitory potential of naldemedine on CYP2E1 and CYP4A11.

Naldemedine and nor-naldemedine produced little/no inhibition of P-gp, BCRP, OCT1, OCT2, MATE1, MATE2-K and BSEP at clinically relevant concentrations *in vitro*. Because the transport activities were not inhibited by more than 50%, it is unlikely that naldemedine and nor-naldemedine will lead to clinically relevant DDIs due to the inhibition of these transporters. *In vitro* data also showed that naldemedine is not a direct inhibitor of OATP1B1, OATP1B3, OAT1 and OAT3 transporters at clinically relevant naldemedine concentrations. However, the lack of the assessment of the impact of a pre-incubation step in the *in vitro* study conducted does not allow determining if a time-dependent inhibition with naldemedine is present or not, while enhanced inhibition of transporters by pre-incubation have been reported in the literature for OATP1B1, OATP1B3, OAT1 and OAT3. The Applicant is therefore recommended to provide further *in vitro* data assessing the impact of an adequate pre-incubation step of at least 30 minutes for OATP1B1 and OATP1B3 and 60 minutes for OAT1 and OAT3 on the inhibitory potential of naldemedine on OATP1B1, OATP1B3 (first 6 months after authorization), OAT1 and OAT3 transporters, taking into account the actual naldemedine concentrations present in the *in vitro* system used.

In Silico

The entirety of available data from Phase 1 studies was considered and new sensitivity analyses were performed. In the CLR range of 1.0 to 2.5 L/hr, AUC ratios of naldemedine following administration of naldemedine with efavirenz relative to naldemedine alone were consistent with the values of 0.555 to 0.580, indicating AUC ratio was not influenced by CLR. However, given the remaining uncertainty in the model and given that SIMCYP plateform is currently not considered qualified for to characterize drug induction (in the absence of in vivo data), the effect of moderate inducers (e.g. efavirenz,) can therefore not be established; therefore, the use of rizmoic acid should cautiously be considered in patients already given a moderate inducer (see SmPC sections 4.4 and 4.5).

In vivo DDI

In general, the limited applicant´s *in vivo* DDI program is considered adequate and was performed according to the guideline on the Investigation of Drug Interactions. The program consists of 3 DDI studies carried out in healthy subjects designed to assess effects of P-gp inhibition, CYP3A induction and inhibition on naldemedine as a substrate.

Based on the study results, it can be concluded that a clinically meaningful effect on naldemedine exposure by itraconazole (strong CYP3A inhibitor) and rifampin (strong inducer) is observed. The strong CYP3A inhibitor Itraconazole increased Cmax, AUC0-last, and AUC0-inf of naldemedine by 1.12 fold, 2.65 fold, and 2.91 fold. The geometric LS mean naldemedine Cmax, AUC0-last, AUC0-inf, and t1/2,z values were approximately 38%, 83%, 83%, and 73% lower, respectively, following Naldemedine:Rifampin compared with Naldemedine alone. The geometric LS mean naldemedine CL/F value was approximately 6-fold following Naldemedine:Rifampin compared with Naldemedine alone, and the 90% CI for the ratio of CL/F was completely outside the 0.80 to 1.25 reference interval. Appropriate statements are made in the SmPC.

Fluconazole increased Cmax, AUC0-last, and AUC0-inf of naldemedine by 1.38 fold, 1.88 fold, and 1.90 fold. Even if it concerns a mild inhibition, caution should be exercised as the number of TEAE increased when naldemedine is administered concomitantly with moderate CYP3A inhibitors in the clinical studies. If used with moderate CYP3A inhibitors, monitoring for adverse reactions is needed as advised in 4.4 of the SmPC.

Cyclosporine as Pg-P inhibitor increased the AUC and Cmax of naldemedine after single-dose administration by 79% and 45% respectively (< 2-fold). The SmPC correctly stated: *Concomitant use of P-gp inhibitors such as cyclosporine may increase plasma concentrations of naldemedine. If naldemedine is used with strong P-gp inhibitors, monitor for adverse reactions.*

Pharmacodynamics:

The pharmacodynamics of naldemedine has not been specifically studied in healthy volunteers or in patients. Naldemedine is antagonist of the μ-, δ-, and κ-opioid receptors, and has no agonistic activity at any of these opioid receptors. The suggested mechanism of action appears plausible based on preclinical studies. From in vitro data, the primary metabolite is much less potent and is less likely to contribute to a clinically meaningful efficacy or adverse reactions.

PK-PD associations has been studied using the Bayesian estimates of AUC from the PoP-PK model and response rate as well as rates of gastrointestinal AEs in phase II and III trials. These results suggest weak to moderate associations between exposure and clinical response or AE. Use of a model-based approach to quantitatively characterize the relationship between drug exposure and clinical efficacy and safety is supported.

An adequately designed, performed and conducted thorough QTC study did not suggest that naldemedine prolongs the QTc interval to a clinically meaningful extent.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of naldemedine has been correctly characterised. No major issues have been identified. The application is considered approvable from a pharmacological viewpoint.

2.5. Clinical efficacy

2.5.1. Dose response studies

There were three dose response studies submitted I this application. The first study, study V9214, was a Phase 2, single-centre, randomised, double-blind, placebo-controlled, single-ascending dose study evaluating 6 dose levels (0.01, 0.03, 0.1, 0.3, 1 and 3 mg) of naldemedine in subjects with chronic non-cancer pain. This study indicated that only doses of 0.3 mg and higher had an effect. Furthermore, doses of 1 and 3 mg were associated with an increase in adverse events.

The second study was study V9221. This was a Phase 2, randomised, double-blind, placebo-controlled, parallel-group study to evaluate 3 doses (0.1, 0.2 and 0.4 mg) of naldemedine in the treatment of OIC in subjects with chronic non-cancer pain. Thus exploring if the dose found to be the minimally effective dose in study V9214 (0.3 mg) would be the most optimal. The mean dose of opioid analgesic was 120-146 mg across treatment groups.

Primary endpoint:

Table 14 Change in the Frequency of Spontaneous Bowel Movements per Week from Baseline to the Last 2 Weeks of the Treatment Period – Modified Intention-to-Treat Population

Time Point Statistic	Placebo (N = 61)	S-297995 0.1 mg (N = 61)	S-297995 0.2 mg (N = 59)	S-297995 0.4 mg (N = 57)
Last 2 weeks of treatment period				
n [a]	61	61	59	57
Baseline mean (SD) [b]	1.22 (0.720)	1.51 (0.820)	1.52 (0.916)	1.20 (0.948)
Endpoint mean (SD) [c]	2.64 (2.234)	3.50 (2.511)	4.90 (4.768)	4.83 (3.526)
Mean change (SD)	1.42 (2.195)	1.99 (2.230)	3.38 (4.725)	3.63 (3.346)
LS mean change (SE) [d]	1.42 (0.422)	1.98 (0.422)	3.37 (0.429)	3.64 (0.437)
Treatment comparison vs. placebo				
Difference in LS mean change (SE) [d]		0.56 (0.599)	1.95 (0.604)	2.22 (0.605)
95% CI for difference [d]		(-0.62, 1.74)	(0.76, 3.14)	(1.02, 3.41)
p-value [d]		0.3504	0.0014	0.0003
Treatment comparison vs. S-297995 0.1 mg				
Difference in LS mean change (SE) [d]			1.39 (0.599)	1.66 (0.610)
95% CI for difference [d]			(0.21, 2.57)	(0.45, 2.86)
p-value [d]			0.0213	0.0071
Treatment comparison vs. S-297995 0.2 mg				
Difference in LS mean change (SE) [d]				0.27 (0.615)
95% CI for difference [d]				(-0.95, 1.48)
p-value [d]				0.6657

a. n is the number of subjects with values at both baseline and the specified endpoint.
b. Baseline is the period from the time on Day -14 to the time of study drug administration on Day 1.
c. Last 2 weeks of the treatment period is the period from 14 days before the last administration day of study drug to the final administration day of study drug.
d. Statistics are from an ANCOVA model with treatment group as a term and baseline value as a covariate.

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error.

Source: Post-text Table 14.2-1.1.1

The third study was a Phase 2, multinational (Japan and Korea), multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate 3 dose levels ((0.1, 0.2 and 0.4 mg) of naldemedine in cancer patients with OIC. The mean daily dose of opioid was 55-85 mg across treatment groups.

Primary endpoint:

Table 15 Analysis of Change in the Frequency of SBM per Week from Baseline to 2-Week Treatment Period - FAS

Time Point Statistic	Placebo N=56	S-297995 0.1 mg N=55	S-297995 0.2 mg N=58	S-297995 0.4 mg N=56
2 weeks of treatment period				
n [a]	56	55	58	56
Baseline mean (SD) [b]	0.99 (0.79)	0.95 (0.82)	1.04 (0.92)	1.06 (0.91)
Endpoint mean (SD) [c]	2.49 (2.95)	4.39 (3.56)	5.79 (3.74)	8.35 (8.35)
Mean change (SD)	1.50 (2.91)	3.44 (3.54)	4.75 (3.73)	7.28 (8.25)
LS mean change (SE) [d]	1.50 (0.68)	3.43 (0.69)	4.75 (0.67)	7.29 (0.68)
Treatment comparison vs. placebo				
Difference in LS mean change (SE) [d]	—	1.93 (0.96)	3.25 (0.95)	5.79 (0.96)
95% CI for difference [d]	—	0.03, 3.83	1.38, 5.13	3.90, 7.68
p-value [d]	—	**0.0465**	**0.0007**	**< 0.0001**
Treatment comparison vs. S-297995 0.1 mg				
Difference in LS mean change (SE) [d]	—	—	1.32 (0.96)	3.86 (0.97)
95% CI for difference [d]	—	—	−0.56, 3.21	1.96, 5.76
p-value [d]	—	—	0.1681	**< 0.0001**
Treatment comparison vs. S-297995 0.2 mg				
Difference in LS mean change (SE) [d]	—	—	—	2.54 (0.95)
95% CI for difference [d]	—	—	—	0.66, 4.41
p-value [d]	—	—	—	**0.0083**

a n is the number of subjects with values at both baseline and the specified endpoint.
b Baseline is the period from the time on Day -14 to the time of study drug administration on Day 1.
c Two weeks of the treatment period is defined as the time from administration of the study drug on Day 1 to the corresponding time on Day 15 or to the time of study discontinuation.
d Statistics are from an ANCOVA model with treatment group as a fixed effect and baseline value as a covariate.
ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error.
Source: Post-text Table 14.2-1.1.1

2.5.2. Main studies

V9231 and V9232

The two trials V9231 and V9232 with the title: "A randomized, double-blind, placebo-controlled, parallel-group study of naldemedine in the treatment of opioid-induced constipation in subjects with non-malignant chronic pain receiving opioid therapy" were identical in design and are described jointly in this section. The trials were randomized, double-blind, placebo-controlled, parallel-group, multicentre, multinational trials comparing efficacy and safety of 0.2 mg QD naldemedine versus placebo. The trials consisted of a 2-4-week screening period, a 12-week treatment period, and a 4-week follow-up period.

At visit 1 subjects were screened to determine eligibility and any laxative treatment was discontinued. At visit 2, 2-4 weeks later, subjects were randomized to treatment with either naldemedine or placebo for 12 weeks. During the treatment period subjects attended 6 scheduled visits: baseline/randomization, Week 1, Week 2, Week 4, Week 8, and Week 12, and completed the Bowel movement and constipation

assessment (BMCA) including the Bristol stool scale (BSS) on a daily basis by entering the data into the eDiary. The patient assessment of constipation symptom/quality of life questionnaires (PAC-SYM/PAC-QOL) was completed at all scheduled treatment visits whereas Short Form 36 was completed at baseline and end of treatment period, and Subject Global Satisfaction was completed at end of treatment period.

Methods

Study Participants

The trials were conducted in patients with chronic non-cancer pain and OIC and investigated the effect of naldemedine as monotherapy.

The main inclusion criteria were

- 18-80 years of age, inclusive
- Diagnosis of chronic non-cancer pain and OIC
- Receiving chronic opioid therapy for at least 3 months

o Opioid regimen stable at a TDD on average of at least 30 mg equivalents of oral morphine sulphate for at least 1 months prior to screening (tramadol and tapentadol not included in calculations, with no anticipated changes in the overall opioid regimen)

- Patients must have met the following 3 criteria over a 14-consecutive-day qualifying period during the screening period:

o No more than 4 SBMs during the 14-consecutive-day qualifying period, and no more than 3 SBMS in a given week of the qualifying period

o One or more of the following bowel symptoms in at least 25% of BMs: presence of straining, lumpy or hard stools, sensation of incomplete evacuation, or sensation of anorectal obstruction/blockage

o Compliance at least 78% with daily completion of eDiary entries during the 14-consecutive-day qualification period (11 days out of the 14)

The main exclusion criteria were

- Subjects who had never taken laxatives for the treatment of OIC
- Severe constipation that has not been appropriately managed such that the subject is at immediate risk of developing serious complications of constipation. This includes subject who have reported no bowel movements for 7 consecutive days prior to and during the screening period.

Laxatives were discontinued at screening.

Trial drug was to be discontinued for any of the following reasons:

- Withdrawal by subject
- On the discretion of the investigator because of safety reasons
- If the subject met the liver discontinuation criteria (abnormal liver chemistry criteria)
- Lost to follow-up
- Pregnancy
- Any protocol deviation that resulted in a significant risk to the subject's safety
- Unblinding

Withdrawal from the trial: subjects may voluntarily withdraw from the trial for any reason at any time. For withdrawn subjects every effort is made to determine the primary reason for withdrawal and record this in the CRF.

Treatments

Patients were randomized 1:1 to receive either naldemedine 0.2 mg QD or placebo tables matching 0.2 mg naldemedine QD orally. Patients were instructed to choose the most appropriate time for daily dosing (i.e. the time associated with the highest compliance and convenience relative to occurrence of BMs) and to take the drug at approximately the same time each day.

Opioid treatment: The stable opioid treatment regimen at a TDD on average of at least 30 mg equivalents of oral morphine sulphate at screening was to be continued throughout the study. Patients were allowed to take additional medication (opioid or non-opioid) for breakthrough pain as prescribed by their physician.

Rescue medication: Rescue laxative therapy according to the Rescue Laxative Guidelines was allowed and could be initiated by the subject, if the subject did not have BM for any 72 hours period during screening or treatment. Step 1 in the Rescue Laxative Guidelines was stimulant laxative (bisacodyl), and if no BM took place within 24 hours, Step 2 was to continue on a higher dose and/or a saline enema. Study drug was continued throughout the study despite whether rescue medication was taken or not. Every attempt was made to limit laxative use during the 24-hour period immediately prior to randomization as time to first SBM was an exploratory endpoint. A BM occurring within 24 hours after rescue therapy was not counted as an SBM.

Objectives

Primary objective: To compare the efficacy assessed over 12 weeks based on the responder proportion of naldemedine 0.2 mg QD versus placebo in subjects with chronic non-cancer pain OIC not treated with laxatives.

Secondary objectives: To compare the effect of naldemedine 0.2 mg QD versus placebo on the frequency of SBMs, CSBMS, and SBMS without straining in subjects with chronic non-cancer pain OIC not treated with laxatives. To evaluate the safety and tolerability of naldemedine.

Outcomes/endpoints

A positive-response week was defined as at least 3 SBMS per week and an increase from baseline of at least 1 SBM per week for that week. The primary endpoint response was defined as having at least 9 positive-response weeks out of the 12-week treatment period, and 3 positive-response weeks out of the last 4 weeks of the 12-week treatment period.

Secondary endpoints were:

1. Change in the frequency of SBMS per week from baseline to the last 2 weeks of the treatment period
2. Change in the frequency of SBMS per week from baseline to week 1 of the treatment period
3. Change in the frequency of CSBM per week from baseline to the last 2 week of the treatment period
4. Change in the frequency of SBMs without straining per week from baseline to the last 2 weeks of the treatment period.

A fixed-sequence testing approach will be applied with the above ordering to adjust for multiplicity.

Exploratory endpoints were:

- Proportion of CSBM responders (definition similar to that of SBM responders)
- Proportion of SBM responders in any 6 weeks
- Proportion of SBM responders in any 9 weeks
- Proportion of SBM monthly responders
- Change in each variable related to defecation per week from baseline to each week of the treatment period
    - Frequency of SBMs with BSS of 3 or 4 per week
    - Frequency of SBMs per week
    - Frequency of CSBMs per week
    - Frequency of SBMs without straining per week
    - Frequency of SBMs without blockage per week
    - Number of days with at least 1 SBM per week
    - Number of days with at least 1 CSBM per week
- Time to the first SBM and CSBM after initial dose of study drug
- Incidence of SBM and CSBM within 4, 8, 12, 24, and 48 hours after initial dose of study drug
- Change in maximal number of days between SBMs from baseline for each 2-week period of the treatment period

- Change in each variable (frequency per week and number of days of) related to rescue laxative use per week from baseline to each week of the treatment period
- Change in the abdominal bloating and abdominal discomfort scores from baseline to each week of the treatment period
- Change form baseline in overall and each domain for patient assessment of constipation symptom/quality of life questionnaires (PAC-SYM/QOL)
- Change from baseline in overall and each domain for Short Form 36
- Frequency of Subject Global Satisfaction
- Changes in total and free testosterone in males

Sample size

Assuming 45% and 30% responders in the naldemedine 0.2 mg group respectively the placebo group for the ITT population, a total of 540 subjects are needed to be randomized in order to have at least 95% power for detecting a more than 15% difference between the two groups for a 2-sided 5% significance level using Pearson's chi-squared test.

Randomisation

At visit 2, eligible patients were randomised in a 1:1 manner to one of the treatment groups using a telephone or web-based randomisation system, IV/WRS. Patients were stratified based on their documented opioid use (average TDD during the 14-consecutive-day qualifying period) (30 to at most 100 mg equivalents of oral morphine sulphate, or more than 100 mg equivalents of oral morphine sulphate).

Blinding (masking)

The trial was a double-blind placebo-controlled trial. Placebo tablets were identical to active tablets in shape and colour.

All subjects, study personnel, and data analysts were blinded to the treatment assigned at randomization until database lock. The randomization schedule was only accessible to Drug Supply Management staff, IVRS/IWRS Clinical coordinators/vendor staff, and unblinded statistician on the Data Safety Monitoring Board.

Statistical methods

Primary endpoint

A responder was defined as having at least 9 positive-response weeks out of the 12-week treatment period, and at least 3 positive-response weeks out of the last 4 weeks of the 12-week treatment period, where a positive-response week defined as at least 3 SBMS per week and an increase from baseline of at least 1 SBM per week for that week. If a subject has less than 4 days of diary entries related to defecation for a week that will week will be considered non-evaluable. For the primary analysis a non-evaluable week will be considered a "non-response" week.

If a subject has insufficient primary endpoint data (i.e. data for less than 9 out of the 12 weeks of the treatment period or less than 3 out of the last 4 weeks of the 12-week treatment period) the subject will be treated as a "non-responder".

A BM occurring within 24 hours after rescue therapy was not counted as an SBM. If the time at which a BM occurred is missing and there is no rescue laxative therapy on the previous day and the day of the BM, the BM will be considered as an SBM. If the time at which a BM occurred is missing and there is rescue laxative therapy on the previous day and the day of the BM, the BM will not be considered as an SBM.

Any number of SBMs rated on the Bristol Stool Scale as 1 within a 2-hour period was counted as a single SBM. A BM occurring within 24 hours after rescue therapy was not counted as an SBM.

The number of SBMs per week in a given week is defined as 7*(total frequency of SBMs in the week)/(Number of days of observation related to defecation in the week), i.e. it is the observed average scaled to a 7-day observation period.

Analysis populations:

ITT: All randomized subjects.

mITT: All randomized subjects who received at least one dose of trial drug and completed the first 4 weeks of the study with at least 4 days of diary entry related to defecations per week. Analysed as randomised.

Safety population: All randomized subjects who received at least one dose of trial drug will be analysed by treatment actually received. Subjects who took naldemedine at least once will be analysed by the naldemedine group.

PP: All subjects who completed at least 81 days of the treatment period and do not have major protocol deviations.

Statistical analysis of primary endpoint: the proportion of responders will be compared for naldemedine versus placebo using the Cochran Mantel Haenszel test adjusted by the stratified opioid dose groups. The population will be the ITT population consisting of all randomized subjects.

Sensitivity analyses:

The same model (stratified Cochran Mantel Haenszel test) will be used in all sensitivity analyses, but the effect of different populations as well as different ways of imputing missing data will be examined as follows:

- Observed case: non-evaluable weeks are excluded from the analysis. Response is defined among the evaluable weeks. A subject who did not have at least 9 evaluable weeks was considered a “non-responder”.
- Complete case: subjects with less than 4 days of diary entries related to defecation at any week are excluded
- Worst case: subjects with missing diary entries related to defecation at any day in a week are considered non-responders for that week
- Modified worst case: for subject with no diary entries related to defecation at any day in a week the number of SBMs for that day are set to 0. However if a treatment week is non-evaluable that week will be treated as a “non-response” week.
- mITT population
- PP population

The different sensitivity analyses are summarized in the table below:

Analysis	SBMs per week [a)]	Non-evaluable week	Handling of non-evaluable week
Primary	(# of SBMs) × 7 / (# of Days of observation)	< 4 days	A non-evaluable week is treated as a non-response week.
Observed case	(# of SBMs) × 7 / (# of Days of observation)	< 4 days	'last 4 weeks' excludes non-evaluable weeks.
Complete case	(# of SBMs) × 7 / (# of Days of observation)	< 4 days	Excludes subjects who have at least one non-evaluable week from the analysis
Worse case	# of SBMs	< 7 days	A non-evaluable week is treated as a non-response week.
Modified Worst case	# of SBMs	< 4 days	A non-evaluable week is treated as a non-response week.
mITT	(# of SBMs) × 7 / (# of Days of observation)	< 4 days	A non-evaluable week is treated as a non-response week.
PP	(# of SBMs) × 7 / (# of Days of observation)	< 4 days	A non-evaluable week is treated as a non-response week.

a) '# of SBMs': Total number of SBMs in the week, '# of Days of observation': Number of days of observation related to defecation in the week

In addition the primary endpoint will also be examined for the following subgroups:

- Opioid dose strata
- Age
- BMI
- Gender
- Race
- Region, country and site

Only descriptive results of the subgroup analyses will be presented.

The family-wise type 1 error rate for the confirmatory secondary endpoints was controlled by using the pre-specified fixed-sequence testing approach with the order

1. Change in the frequency of SBMs per week from baseline to the last 2 weeks of the treatment period
2. Change in the frequency of SBMs per week from baseline to week 1 of the treatment period
3. Change in the frequency of CSBM per week from baseline to the last 2 week of the treatment period
4. Change in the frequency of SBMs without straining per week from baseline to the last 2 weeks of the treatment period.

For secondary and exploratory endpoints the same definition of frequency of SBMS per week as for the primary analysis is applied, i.e. the frequency of SBMs per week is defined as 7*(total frequency of SBMs in the week)/(Number of days of observation related to defecation in the week). And in analogy with this the weekly frequency of SBMs for the last two weeks is given by 7*(total frequency of SBMS in the last two weeks)/(Number of days of observation related to defecation in the week).

If a subject has less than 4 days of diary entries related to defecation in a week that week will be considered non-evaluable and the missing information will not be imputed.

Statistical analysis of secondary endpoints: the mean of the change in the relevant endpoint will be analysed using analysis of covariate (ANCOVA) with treatment and opioid group strata as factors. The population will be the ITT population consisting of all randomized subjects.

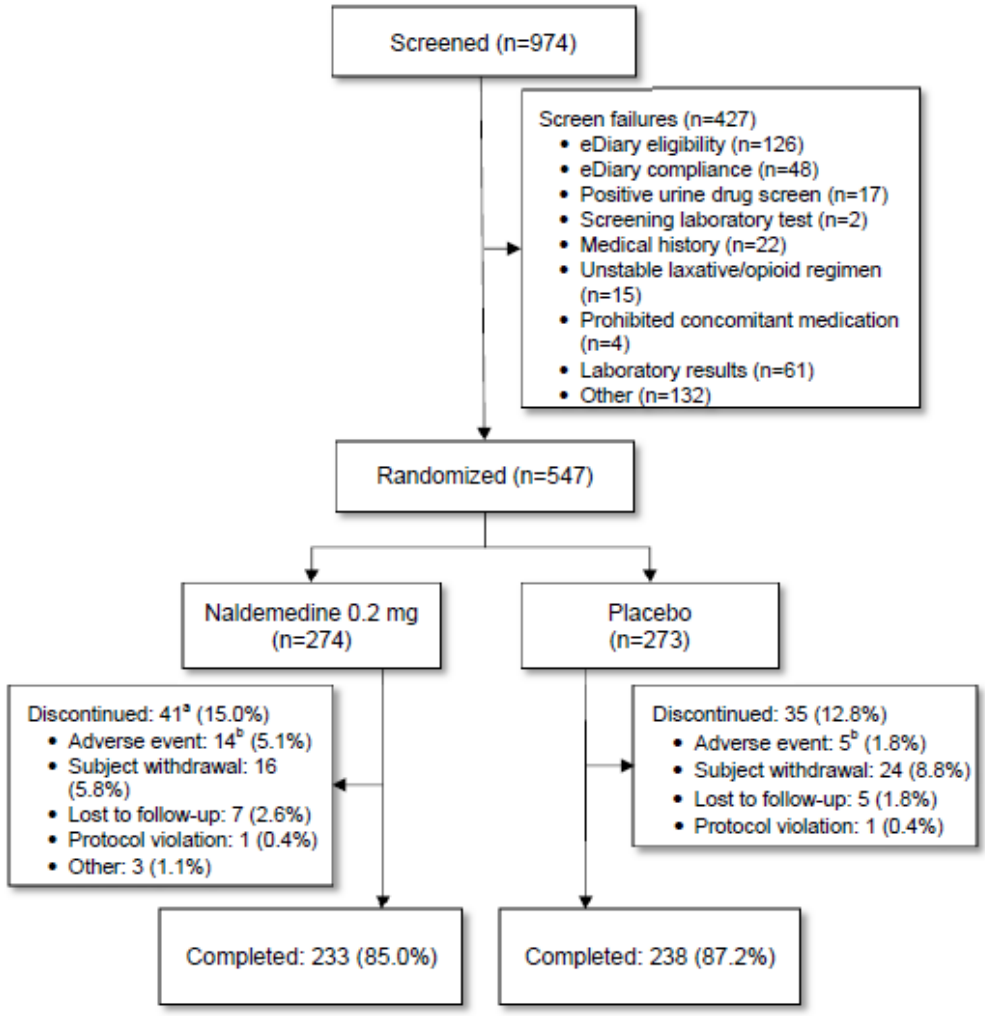
Statistical analysis of exploratory endpoints:

Analysis of responder endpoints will be done similarly to the primary analysis. Analysis of changes in frequencies per week will be done using MMRM including opioid group strata, treatment group, time, and time-by-treatment group interaction as fixed factors. An unstructured covariance matrix within subjects will be assumed. The population will be the ITT population consisting of all randomized subjects.

Results

Participant flow

V9231:
A total of 974 subjects were screened. Out of these 427 (44%) failed screening mainly due to eDiary eligibility and Other, resulting in a total of 547 subjects randomised, 274 to naldemedine and 273 to placebo with respectively 233 (85.0%) and 238 (87.2%) completing the study. Subject withdrawal was the main reason for discontinuation followed by adverse events, which was more common for subjects on naldemedine (5.1% compared to 1.8%). In the naldemedine group 8 subjects withdrew due to AEs in the gastrointestinal disorders SOC, compared to 3 subjects in the placebo group. Apart from this reasons for withdrawal seemed balanced and completion rates comparable and reasonably high.



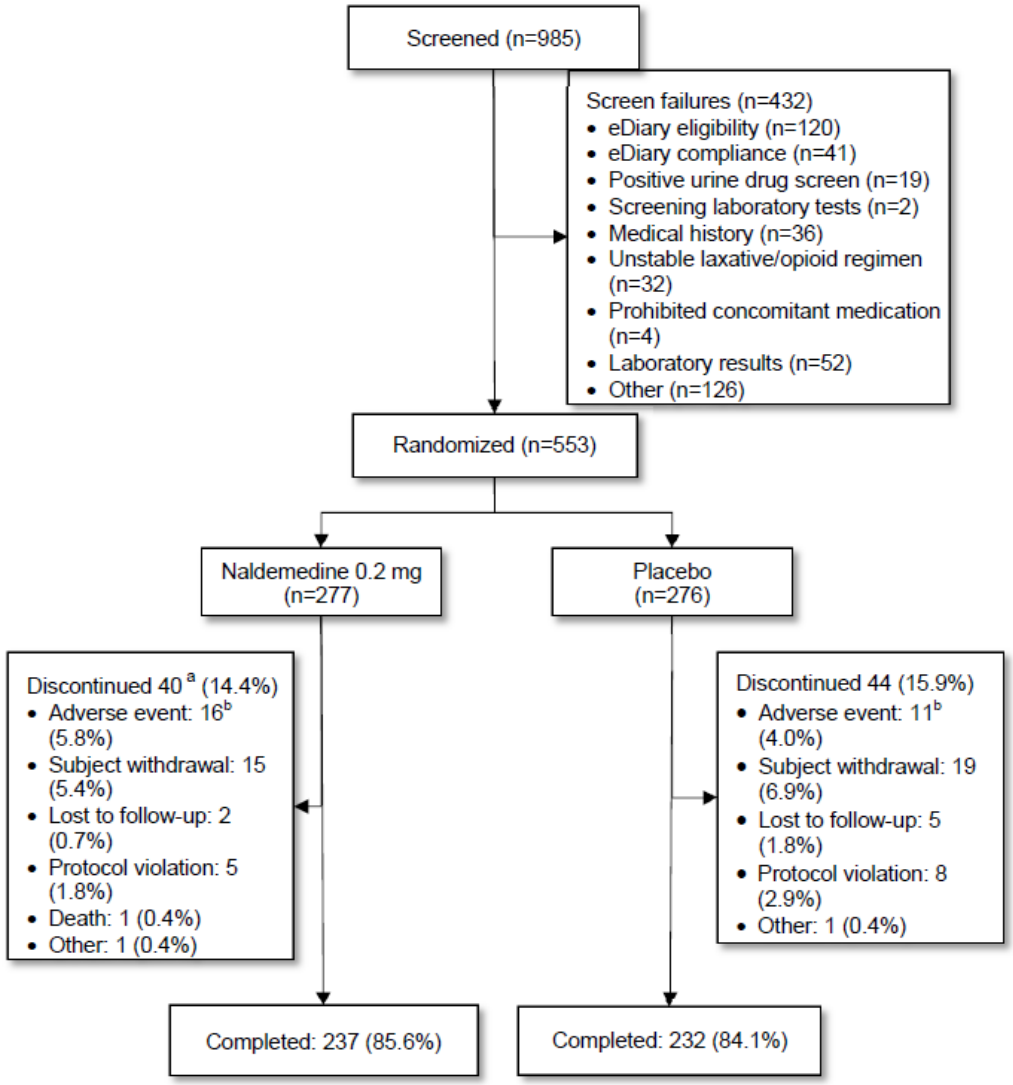
[a] Includes 2 subjects who were randomized but not dosed.

[b] Includes 1 subject discontinued due to an AE with onset prior to the first dose of study drug

eDiary = electronic diary.

V9232:

A total of 985 subjects were screened. Out of these 432 (44%) failed screening mainly due to eDiary eligibility and Other, resulting in a total of 553 subjects randomised, 277 to naldemedine and 276 to placebo with respectively 237 (85.6%) and 232 (84.1%) completing the study. Subject withdrawal was the main reason for discontinuation followed by adverse events, which was more common for subjects on naldemedine (5.8% compared to 4.0%). In the naldemedine group 10 subjects withdrew due to AEs in the gastrointestinal disorders SOC, compared to 4 subjects in the placebo group. Apart from this reasons for withdrawal seemed balanced and completion rates comparable and reasonably high.



[a] Includes 5 subjects who were randomized but not dosed.

[b] Includes 2 subjects discontinued due to an AE with onset prior to the first dose of study drug.

Recruitment

V9231:

The trial was a multicentre trial with 68 trial sites in 7 countries (Austria, Czech Republic, Germany, Poland, Spain, United Kingdom, and the US). The first subject was enrolled in November 2013 and the last subject completed in June 2015.

V9232:

The trial was a multicentre trial with 69 trial sites in 6 countries (Austria, Czech Republic, Germany, Poland, Spain, and the US). The first subject was enrolled in November 2013 and the last subject completed in June 2015.

Conduct of the study

V9231:

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice.

There were 3 amendments to the protocol. The original protocol dated 19 June 2013 was amended on 04 October 2013 (Amendment 1), 11 June 2014 (Amendment 2), and 16 October 2014 (Amendment 3). The key changes in amendment 1 were added clarification of BMCA inclusion criteria, added text to clarify eligibility criteria based on SBMs, changed text to clarify the steps taken for rescue laxative therapy, and added text to allow for Investigator discretion on medication that may have had a significant impact on the GI system or bowel habits. Key changes in amendment 2 were clarification of allowed laxatives during the follow-up period, redefined allowable use of tramadol and tapentadol for clarity, and revised time points for primary efficacy endpoints. Key changes in amendment 3 were revision of secondary endpoints to provide a more thorough clinical efficacy summary of naldemedine including effects from baseline to endpoint, baseline to the first week, straining, and CSBMs, addition of an exploratory endpoint to further assess the effect on SBMs without straining over time, removal of PK assessment as an exploratory endpoint, change of the definition of the mITT Population to produce a population that more accurately accounted for challenges encountered by subjects required to use an electronic data capture tool, modification of the Safety Population to be more inclusive in order to obtain a larger population, and clarification of the definition of insufficient primary endpoint data and a “non-response” week.

V9232:

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice. There we 2 amendments to the protocol. The original protocol dated 04 October 2013 was amended on 11 June 2014 (Amendment 1) and 16 October 2014 (Amendment 2). The key changes in amendment 1 were added clarification of discontinuing regular use of laxatives at start of screening and through the 12-week treatment period, clarification of stratification based on morphine-equivalent dosing as well as redefined allowable use of tramadol and tapentadol, clarification of exclusion criteria related to severe constipation prior to and during the screening period, and clarification of primary efficacy endpoint related to last observation carried forward. The key changes in amendment 2 were the same as the key changes in amendment 3 in V9231.

Baseline data

V9231:

The demographic characteristics of the ITT population were generally well balanced across treatment groups. The mean age was 53.4 years with 74.9% of subjects being between 40 and 65 years, and 15.8% 65 years or above. The majority of patients were female (60.5%) and predominantly White (80.1%) followed by Black/African American subjects (18.5%). The subjects were mainly from North America (84.2%). The study population had a mean weight of 89.91 kg, and the majority of subjects (approximately 80%) were overweight or obese (BMI above 25 kg/m2).

At baseline, the mean daily dose of the opioid analgesic was 125.21 mg morphine-equivalent for the naldemedine group and 139.66 mg morphine-equivalent for the placebo group. The observed difference between groups in the mean opioid dose was driven by a few outliers in the placebo group receiving an opioid morphine-equivalent dose >400 mg. When the mean daily dose at baseline was calculated for subjects taking up to 400 mg, no difference between groups was observed. The mean SBMs per week was 1.31 with a median of 1.50. The majority of subjects (56.5%) were in the low opioid dose strata.

All subjects in the ITT population had constipation and a non-malignant chronic pain condition requiring treatment with opioids. The most commonly reported chronic pain conditions were back pain (62.0%), pain (5.3%), arthralgia (5.1%), neck pain (8.3%), and osteoarthritis (5.3%). The most common reported medical history condition were back pain (66.7%), hypertension (48.6%), and depression (39.6%).

V9232:

The demographic characteristics of the ITT population were generally well balanced across treatment groups. The mean age was 53.5 years with 73.8% of subjects being between 40 and 65 years, and 14.9% 65 years or above. The majority of patients were female (60.5%) and predominantly White (81.6%) followed by Black/African American subjects (16.0%). The subjects were mainly from North America (87.3%). The study population had a mean weight of 89.15 kg, and the majority of subjects (approximately 80%) were overweight or obese (BMI above 25 kg/m2).

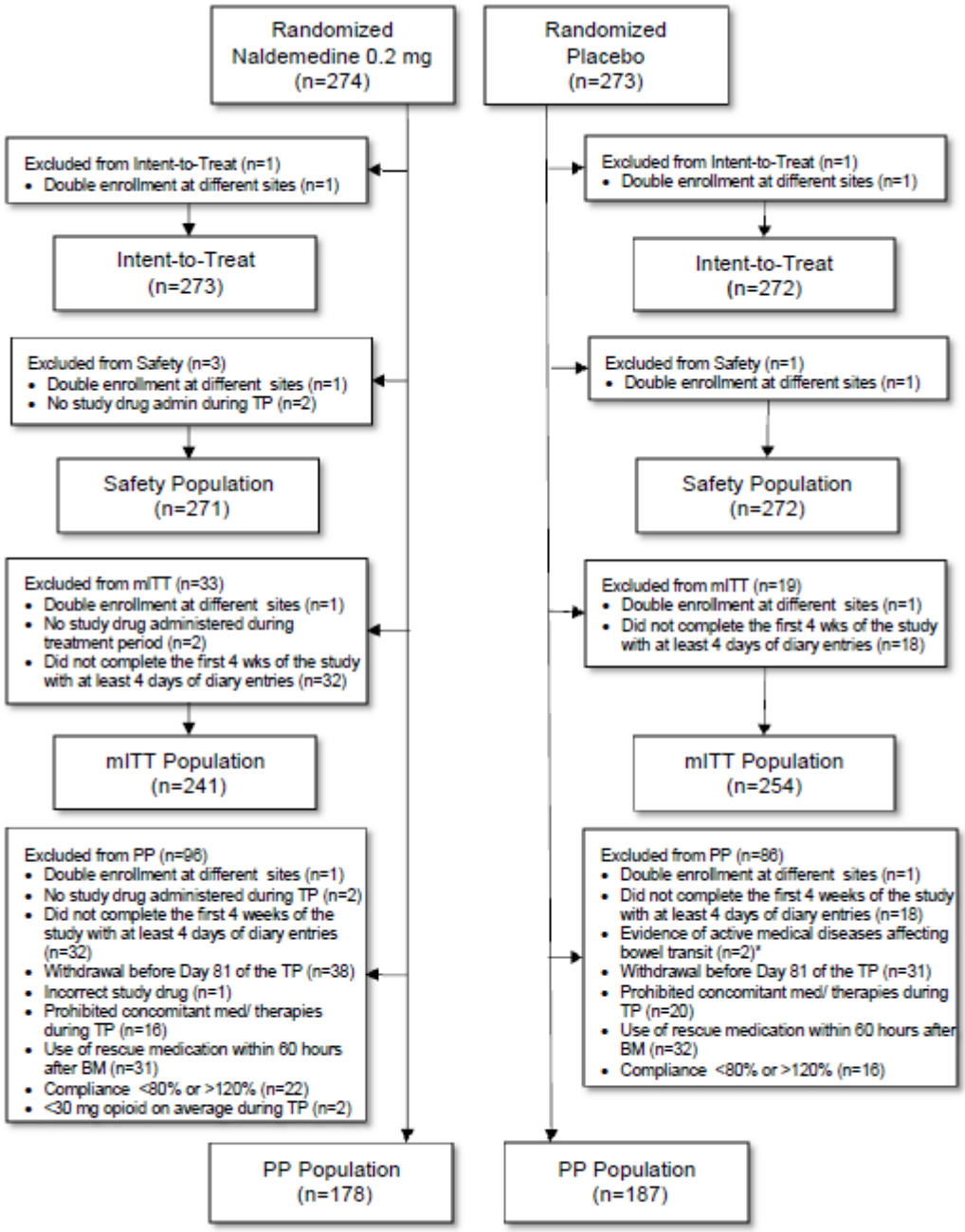
At baseline, the mean daily dose of the opioid analgesic was 117.95 mg morphine-equivalent for the naldemedine group and 123.92 mg morphine-equivalent for the placebo group. The mean SBMs per week was 1.17 with a median of 1.08. The majority of subjects (61.1%) were in the low opioid dose strata.

All subjects in the ITT population has constipation and a non-malignant chronic pain condition requiring treatment with opioids. The most commonly reported chronic pain conditions were back pain (53.6%), pain (10.2%), arthralgia (7.8%), neck pain (7.5%), and osteoarthritis (6.9%). The most common reported medical history condition were back pain (63.8%), hypertension (48.5%), and depression (44.7%).

Numbers analysed

V9231:

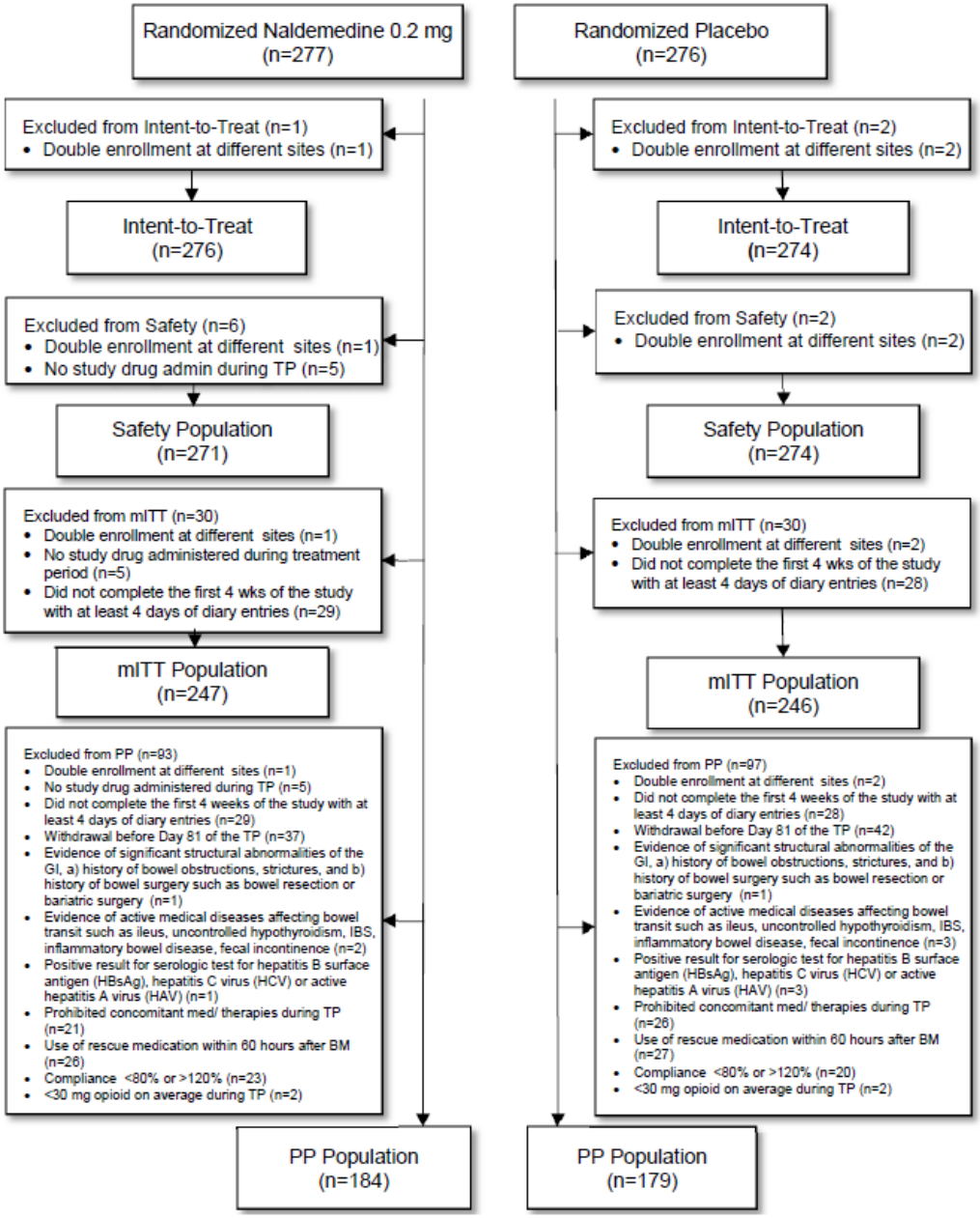
A total of 547 subjects were randomised, 274 to naldemedine and 273 to placebo. One subject in each treatment group was excluded from all populations due to double enrolment at different sites. All other subjects were included in the ITT population. For the Safety Population two additional subjects in the naldemedine group was excluded as they never received trial drug. Several subjects were excluded from the mITT and the PP population, the reasons are given in the flowchart below.



Note: the excluded total in any population may not equal the total of the reasons for exclusion in that population due to subjects being counted in multiple categories.
BM = bowel movement; mITT = modified intent-to-treat; PP = per protocol; TP = treatment period.

V9232:

A total of 553 subjects were randomised, 277 to naldemedine and 276 to placebo. One subject in the naldemedine group and two subjects in the placebo group were excluded from all populations due to double enrolment at different sites. All other subjects were included in the ITT population. For the Safety Population five additional subjects in the naldemedine group was excluded as they never received trial drug. Several subjects were excluded from the mITT and the PP population, the reasons are given in the flowchart below.



Note: the excluded total in any population may not equal the total of the reasons for exclusion in that population due to subjects being counted in multiple categories.
BM = bowel movement; mITT = modified intent-to-treat; PP = per protocol; TP = treatment period.

Outcomes and estimation

Primary analysis

V9231:

The study met its primary endpoint by showing that treatment with naldemedine resulted in a significantly larger proportion responders than treatment with placebo (p=0.0020). The difference in proportion of responders was 13.0%.

Table 11-1 Proportion of Responders: Primary Analysis – Intent-to-Treat Population

		Naldemedine 0.2 mg N=273	Placebo N=272
Responder	Total	47.6 % (130/273)	34.6 % (94/272)
	95% Confidence Interval (%) [a]	41.6, 53.7	28.9, 40.5
Comparison with Placebo	Difference of Proportion (SE) [b]	13.0 (4.19)	
	95% Confidence Interval for Difference	4.8, 21.3	
	P-value [c]	0.0020	

SBM responders were defined as having >=3 SBM /week (on average) with >=1 SBM/week (on average) increase over baseline for >=9 of 12 weeks and >=3 of the last 4 weeks. However, if a subject had less than 4 days of diary entries related to defecation for a week, that week was treated as a 'non-response' week.

[a] Clopper-Pearson method

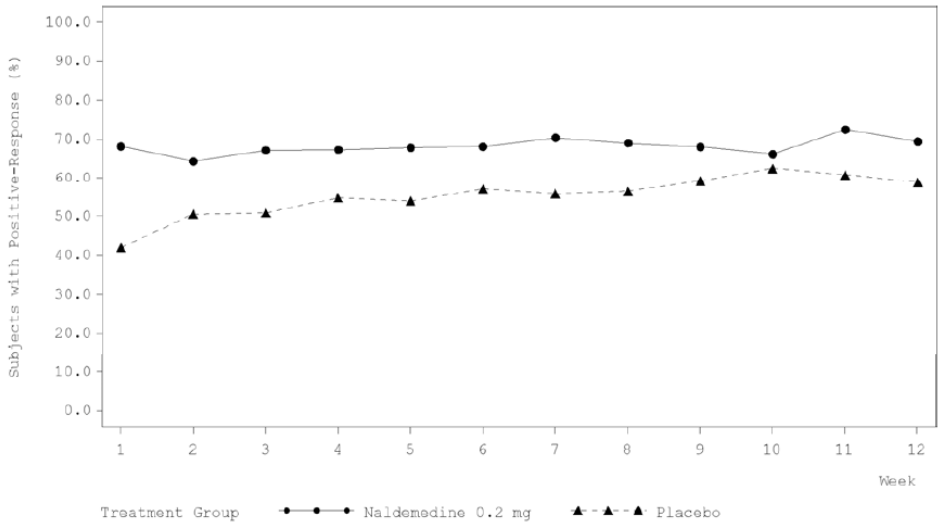
[b] Difference of Proportion (SE) was calculated by using the estimator given by Koch et al[8].

[c] P-value was calculated by Cochran-Mantel-Haenszel test adjusted by the opioid dose strata.

SBM = spontaneous bowel movement; SE = standard error.

Source: Table 14.2-1.1.1

Figure 14.2-1.1.3 Proportion of Subjects with Positive-Response by Week
ITT Population



The denominator was the number of subjects who have at least 4 days of diary entries related to defecation in that week.

V9232:

The study met its primary endpoint by showing that treatment with naldemedine resulted in a significantly larger proportion responders than treatment with placebo (p=<0.0001). The difference in proportion of responders was 18.9%.

Table 11-1 Proportion of Responders: Primary Analysis – Intent-to-Treat Population

		Naldemedine 0.2 mg N=273	Placebo N=272
Responder	Total	47.6 % (130/273)	34.6 % (94/272)
	95% Confidence Interval (%) [a]	41.6, 53.7	28.9, 40.5
Comparison with Placebo	Difference of Proportion (SE) [b]	13.0 (4.19)	
	95% Confidence Interval for Difference	4.8, 21.3	
	P-value [c]	0.0020	

SBM responders were defined as having >=3 SBM /week (on average) with >=1 SBM/week (on average) increase over baseline for >=9 of 12 weeks and >=3 of the last 4 weeks. However, if a subject had less than 4 days of diary entries related to defecation for a week, that week was treated as a 'non-response' week.

[a] Clopper-Pearson method

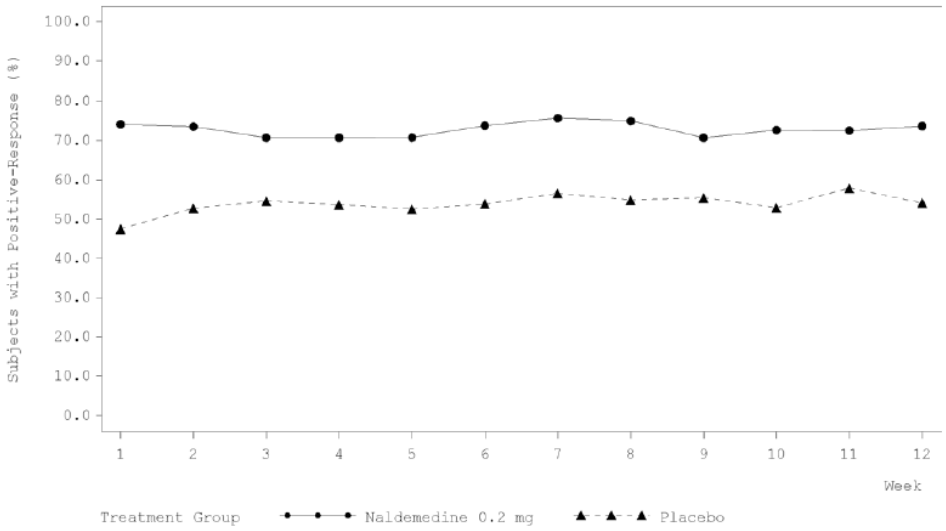
[b] Difference of Proportion (SE) was calculated by using the estimator given by Koch et al[8].

[c] P-value was calculated by Cochran-Mantel-Haenszel test adjusted by the opioid dose strata.

SBM = spontaneous bowel movement; SE = standard error.

Source: Table 14.2-1.1.1

Figure 14.2-1.1.3 Proportion of Subjects with Positive-Response by Week
ITT Population



The denominator was the number of subjects who have at least 4 days of diary entries related to defecation in that week.

Sensitivity analyses

The following sensitivity analyses were pre-defined

Analysis	SBMs per week [a)]	Non-evaluable week	Handling of non-evaluable week
Primary	(# of SBMs) × 7 / (# of Days of observation)	< 4 days	A non-evaluable week is treated as a non-response week.
Observed case	(# of SBMs) × 7 / (# of Days of observation)	< 4 days	'last 4 weeks' excludes non-evaluable weeks.
Complete case	(# of SBMs) × 7 / (# of Days of observation)	< 4 days	Excludes subjects who have at least one non-evaluable week from the analysis
Worse case	# of SBMs	< 7 days	A non-evaluable week is treated as a non-response week.
Modified Worst case	# of SBMs	< 4 days	A non-evaluable week is treated as a non-response week.
mITT	(# of SBMs) × 7 / (# of Days of observation)	< 4 days	A non-evaluable week is treated as a non-response week.
PP	(# of SBMs) × 7 / (# of Days of observation)	< 4 days	A non-evaluable week is treated as a non-response week.

a) '# of SBMs': Total number of SBMs in the week, '# of Days of observation': Number of days of observation related to defecation in the week

V9231:

Summary of the primary analysis and the sensitivity analyses:

Analysis	Treatment difference in proportion of responders (95% CI)	p-value
Primary	13.0% [4.8%; 21.3%]	0.0020
Observed case	13.4% [5.2%; 21.6%]	0.0015
Complete case	17.0% [7.7%; 26.3%]	0.0004
Worst case	9.4% [1.4%; 17.4%]	0.0220
Modified Worst case	12.7% [4.5%; 20.9%]	0.0026
mITT	17.2% [8.6%; 25.9%]	0.0001
PP	14.9% [4.7%; 25.1%]	0.0045

All sensitivity analyses showed a statistically significant greater proportion of responders with naldemedine compared to placebo. The treatment difference ranged from 9.4% (Worst case sensitivity

analysis) to 17.2% (mITT sensitivity analysis). All sensitivity analyses confirm that a higher proportion of subjects respond for naldemedine compared to placebo. But there is almost a 2-fold difference between the lowest and the highest estimated treatment difference. Thus the results of the primary analysis does not seem to be very robust.

V9232:

Summary of the primary analysis and the sensitivity analyses:

Analysis	Treatment difference in proportion of responders (95% CI)	p-value
Primary	18.9% [10.8%; 27.0%]	<0.0001
Observed case	18.9% [10.8%; 27.0%]	<0.0001
Complete case	20.7% [11.5%; 29.9%]	<0.0001
Worst case	13.9% [5.9%; 21.8%]	0.0007
Modified Worst case	19.3% [11.2%; 27.4%]	<0.0001
mITT	20.3% [11.7%; 28.9%]	<0.0001
PP	19.8% [9.8%; 29.9%]	0.0001

All sensitivity analyses showed a statistically significant greater proportion of responders with naldemedine compared to placebo. The treatment difference ranged from 13.9% (Worst case sensitivity analysis) to 20.7% (complete case sensitivity analysis). All sensitivity analyses confirm that a higher proportion of subjects respond for naldemedine compared to placebo and are well in line apart from the worst case scenario which is an outliner as could be expected. Thus the results of the primary analysis seem to be robust.

Subgroup analysis of the primary endpoint

The primary endpoint was investigated in the subgroups opioid dose strata, age, BMI, gender, race, region, country and site.

V9231:

For all subgroups apart from age, the proportion of responders was higher for naldemedine than placebo in consistence with the result of the primary analysis. The results for age were presented for the four groups below 40, 40 to 65, above 65, and above 75 years:

		Naldemedine 0.2 mg N=273	Placebo N=272
Age (years)	<40	36.0 % (9/25)	50.0 % (13/26)
	>=40 to <65	50.2 % (105/209)	33.7 % (67/199)
	>=65	41.0 % (16/39)	29.8 % (14/47)
	>=75	33.3 % (2/6)	25.0 % (2/8)

In all groups apart from below 40 years, the proportion is higher for naldemedine than placebo. There seems to be a tendency that response decreases with age. This is especially true for the placebo group, but for the naldemedine group the response proportion is lower in the age less than 40 years group than

expected, and also lower than the response proportion in the placebo group. The Applicant points out that 8 of the 25 subjects in the naldemedine group discontinued before week 11, hence were classified as non-responders, whereas this only was the case for 3 out of 26 subjects in the placebo group. Also considering that the placebo response proportion was unusually high in the below 40 years group, the applicant considers this a chance finding.

V9232:

For most subgroups the proportion of responders was higher for naldemedine than placebo in consistence with the result of the primary analysis. The exceptions were subjects 75 years or above, subjects with BMI<18.5, and subjects of Black/African American race. There were only few subjects in the subgroups age 75 years or above, and BMI<18.5 not allowing for adequate comparison between groups. For the subgroup of Black/African Americans 7 out of 49 subjects in the naldemedine and 4 out of 39 subjects in the placebo group discontinued prior to *Week 11, and hence were non-responders. Also the responder proportion in the placebo group was among the highest observed, whereas the responder proportion in the naldemedine group was among the lowest observed. Thus the applicant considers this a chance finding.

Table 11-3 Proportion of Responders by Baseline Demographic Characteristics – Intent-to-Treat Population

		Naldemedine 0.2 mg N=276	Placebo N=274
Race	AMERICAN INDIAN OR ALASKA NATIVE	66.7 % (2/3)	25.0 % (1/4)
	ASIAN	100.0 % (2/2)	66.7 % (2/3)
	BLACK OR AFRICAN AMERICAN	40.8 % (20/49)	46.2 % (18/39)
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	---	0.0 % (0/1)
	WHITE	54.5 % (121/222)	31.3 % (71/227)

Secondary efficacy endpoints

The secondary endpoints were defined in the below fixed-sequence order:

1. Change in the frequency of SBMs per week from baseline to the last 2 weeks of the treatment period
2. Change in the frequency of SBMs per week from baseline to week 1 of the treatment period
3. Change in the frequency of CSBM per week from baseline to the last 2 week of the treatment period
4. Change in the frequency of SBMs without straining per week from baseline to the last 2 weeks of the treatment period.

V9231:

The results were:

1. A greater change in the frequency of SBMs per week from baseline to the last 2 weeks of treatment for naldemedine than placebo, treatment difference of 1.30 SBMs per week ($p<0.0001$).
2. A greater change in the frequency of SBMs per week from baseline to the Week 1 for naldemedine than placebo, treatment difference of 2.11 SBMs per week ($p<0.0001$).

3. A greater change in the frequency of CSBMs per week from baseline to the last 2 weeks of treatment for naldemedine than placebo, treatment difference of 1.01 CSBMs per week ($p<0.0001$).
4. A greater change in the frequency of SBMs without straining per week from baseline to the last 2 weeks of treatment for naldemedine than placebo, treatment difference of 0.73 SBMs per week ($p=0.0003$).

Note that all hypotheses were rejected, hence the fixed-sequence order testing continued throughout the entire sequence. The detailed results are seen below:

Table 11-4 Change in the Frequency of Spontaneous Bowel Movements per Week from Baseline to Last 2 Weeks – Intent-to-Treat Population

Time Point	Statistic	Naldemedine 0.2 mg N=273	Placebo N=272
Baseline	Mean (SD)	1.31 (0.746)	1.30 (0.713)
Last Two Weeks	Mean (SD)	4.77 (3.768)	3.44 (2.470)
- Parameter estimates	LS Mean (SE)	3.42 (0.193)	2.12 (0.192)
- Comparison with Placebo	Difference of LS Mean (SE)	1.30 (0.271)	
	95% CI for Difference	0.77, 1.83	
	P-value	<.0001	

The ANCOVA model has the terms for treatment group as a fixed effect and the opioid dose strata as a covariate.
ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error.

Table 11-5 Change in the Frequency of Spontaneous Bowel Movements per Week from Baseline to Week 1 – Intent-to-Treat Population

Time Point	Statistic	Naldemedine 0.2 mg N=273	Placebo N=272
Baseline	Mean (SD)	1.31 (0.746)	1.30 (0.713)
Week 1	Mean (SD)	4.77 (3.889)	2.64 (2.045)
- Parameter estimates	LS Mean (SE)	3.48 (0.185)	1.36 (0.184)
- Comparison with Placebo	Difference of LS Mean (SE)	2.11 (0.260)	
	95% CI for Difference	1.60, 2.63	
	P-value	<.0001	

The ANCOVA model has the terms for treatment group as a fixed effect and the opioid dose strata as a covariate.
ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error.

Table 11-6 Change in the Frequency of Complete Spontaneous Bowel Movements per Week from Baseline to the Last 2 Weeks – Intent-to-Treat Population

Time Point	Statistic	Naldemedine 0.2 mg N=273	Placebo N=272
Baseline	Mean (SD)	0.40 (0.596)	0.38 (0.567)
Last Two Weeks	Mean (SD)	3.00 (3.374)	1.97 (2.146)
- Parameter estimates	LS Mean (SE)	2.58 (0.170)	1.57 (0.170)
- Comparison with Placebo	Difference of LS Mean (SE)	1.01 (0.240)	
	95% CI for Difference	0.54, 1.48	
	P-value	<.0001	

The ANCOVA model has the terms for treatment group as a fixed effect and the opioid dose strata as a covariate.
ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error.

Table 11-7 Change in the Frequency of Spontaneous Bowel Movements without Straining per Week from Baseline to the Last 2 Weeks – Intent-to-Treat Population

Time Point	Statistic	Naldemedine 0.2 mg N=273	Placebo N=272
Baseline	Mean (SD)	0.11 (0.313)	0.08 (0.304)
Last Two Weeks	Mean (SD)	1.57 (2.766)	0.82 (1.699)
- Parameter estimates	LS Mean (SE)	1.46 (0.141)	0.73 (0.140)
- Comparison with Placebo	Difference of LS Mean (SE)	0.73 (0.198)	
	95% CI for Difference	0.34, 1.12	
	P-value	0.0003	

The ANCOVA model has the terms for treatment group as a fixed effect and the opioid dose strata as a covariate.
ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error.

V9232:

The results were:

1. A greater change in the frequency of SBMs per week from baseline to the last 2 weeks of treatment for naldemedine than placebo, treatment difference of 1.40 SBMs per week ($p<0.0001$).
2. A greater change in the frequency of SBMs per week from baseline to the Week 1 for naldemedine than placebo, treatment difference of 2.17 SBMs per week ($p<0.0001$).
3. A greater change in the frequency of CSBMs per week from baseline to the last 2 weeks of treatment for naldemedine than placebo, treatment difference of 1.15 CSBMs per week ($p<0.0001$).
4. A greater change in the frequency of SBMs without straining per week from baseline to the last 2 weeks of treatment for naldemedine than placebo, treatment difference of 0.75 SBMs per week ($p=0.0011$).

Note that all hypotheses were rejected, hence the fixed-sequence order testing continued throughout the entire sequence. The detailed results are seen below:

Table 11-4 Change in the Frequency of Spontaneous Bowel Movements per Week from Baseline to Last 2 Weeks – Intent-to-Treat Population

Time Point	Statistic	Naldemedine 0.2 mg N=276	Placebo N=274
Baseline	Mean (SD)	1.16 (0.755)	1.17 (0.730)
Last Two Weeks	Mean (SD)	4.84 (3.205)	3.44 (2.611)
- Parameter estimates	LS Mean (SE)	3.56 (0.174)	2.16 (0.174)
- Comparison with Placebo	Difference of LS Mean (SE)	1.40 (0.243)	
	95% CI for Difference	0.92, 1.88	
	P-value	<.0001	

The ANCOVA model has the terms for treatment group as a fixed effect and the opioid dose strata as a covariate.

Table 11-5 Change in the Frequency of Spontaneous Bowel Movements per Week from Baseline to Week 1 – Intent-to-Treat Population

Time Point	Statistic	Naldemedine 0.2 mg N=276	Placebo N=274
Baseline	Mean (SD)	1.16 (0.755)	1.17 (0.730)
Week 1	Mean (SD)	5.06 (3.952)	2.89 (2.457)
- Parameter estimates	LS Mean (SE)	3.86 (0.199)	1.69 (0.198)
- Comparison with Placebo	Difference of LS Mean (SE)	2.17 (0.277)	
	95% CI for Difference	1.63, 2.71	
	P-value	<.0001	

The ANCOVA model has the terms for treatment group as a fixed effect and the opioid dose strata as a covariate.

Table 11-6 **Change in the Frequency of Complete Spontaneous Bowel Movements per Week from Baseline to the Last 2 Weeks – Intent-to-Treat Population**

Time Point	Statistic	Naldemedine 0.2 mg N=276	Placebo N=274
Baseline	Mean (SD)	0.35 (0.513)	0.40 (0.560)
Last Two Weeks	Mean (SD)	3.19 (3.095)	2.08 (2.542)
- Parameter estimates	LS Mean (SE)	2.77 (0.166)	1.62 (0.166)
- Comparison with Placebo	Difference of LS Mean (SE)	1.15 (0.232)	
	95% CI for Difference	0.70, 1.61	
	P-value	<.0001	

The ANCOVA model has the terms for treatment group as a fixed effect and the opioid dose strata as a covariate.

Table 11-7 **Change in the Frequency of Spontaneous Bowel Movements without Straining per Week from Baseline to the Last 2 Weeks – Intent-to-Treat Population**

Time Point	Statistic	Naldemedine 0.2 mg N=276	Placebo N=274
Baseline	Mean (SD)	0.08 (0.269)	0.13 (0.375)
Last Two Weeks	Mean (SD)	2.00 (2.986)	1.29 (2.349)
- Parameter estimates	LS Mean (SE)	1.85 (0.163)	1.10 (0.162)
- Comparison with Placebo	Difference of LS Mean (SE)	0.75 (0.227)	
	95% CI for Difference	0.30, 1.19	
	P-value	0.0011	

The ANCOVA model has the terms for treatment group as a fixed effect and the opioid dose strata as a covariate.

Exploratory efficacy evaluation

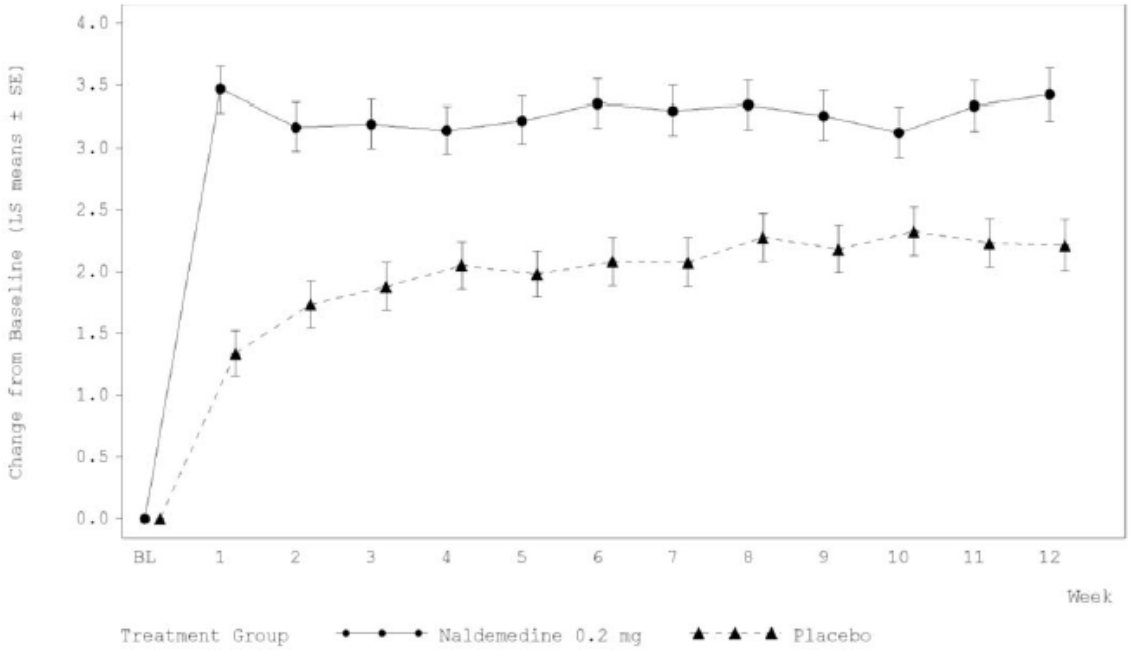
Note that the below analyses were not multiplicity adjusted, hence statistically significance only refers to nominal p-values.

V9231:

- For CSBM a responder was defined similar to a responder for SBM. The proportion of responders was 24.9% for naldemedine and 14.3% for placebo with a statistically significant difference between groups.
- When a responder was defined as a subject with at least **6** positive-response weeks out of the 12-week treatment period (with the usual definition of response-week), the proportion of responders was 63.4% for naldemedine and 55.1% for placebo with a statistically non-significant difference between groups.
- When a responder was defined as a subject with at least **9** positive-response weeks out of the 12-week treatment period (with the usual definition of response-week), the proportion of responders was 52.0% for naldemedine and 35.71% for placebo with a statistically significant difference between groups.
- When a responder was defined as a subject with at least **3** positive-response weeks out of the 4 weeks in a month (with the usual definition of response-week), the proportion of monthly responders for naldemedine and placebo were 58.1% and 40.7% for Month 1, 63.3% and 46.5% for Month 2, and 60.3% and 53.1% for Month 3. The difference between groups was statistically significant for the first two months, but not for the last month.
- Changes over time in the frequency of SBMS per week from baseline increased at Week 1 more for naldemedine than for placebo, and this difference between groups first declined slightly and

then remained stable throughout Week 12 with a statistically significant difference between groups at all time points. See the plot below.

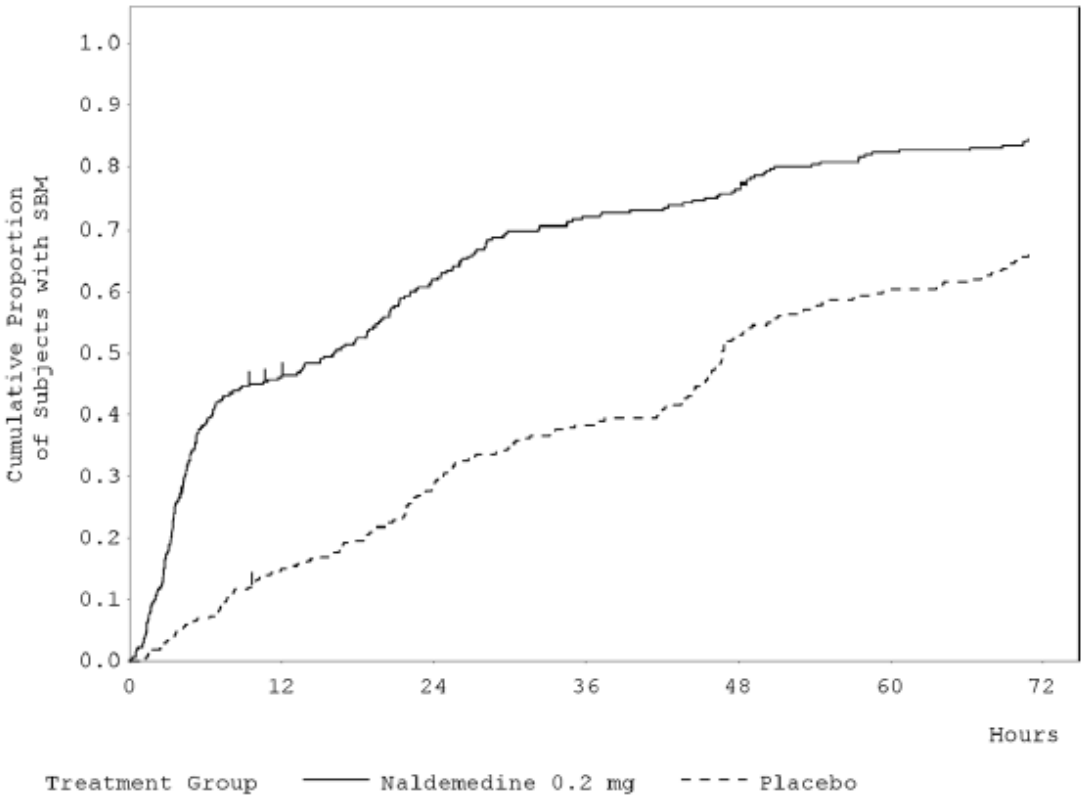
Figure 11-1 Change in the Frequency of Spontaneous Bowel Movements per Week from Baseline to Each Week (Least-Squares Mean ±Standard Error) – Intent-to-Treat Population



Baseline (BL) was 14 consecutive calendar day qualifying period during the Screening Period.
LS = least squares; SE = standard error.

- Changes in the 6 other parameters: frequency of SBMs rated as 3 or 4 on the BSS per week, frequency of CSBMs per week, frequency of SBMs without straining per week, frequency of SBMs without blockage per week, number of days with at least 1 SBM per week, and number of days with at least 1 CSBM per week showed the same pattern as the results for change from baseline over time in the frequency of SBMs per week.
- Median time to first SBM was 16.07 hours for the naldemedine group and 46.73 hours for the placebo group, the difference being statistically significant. See the plot below.

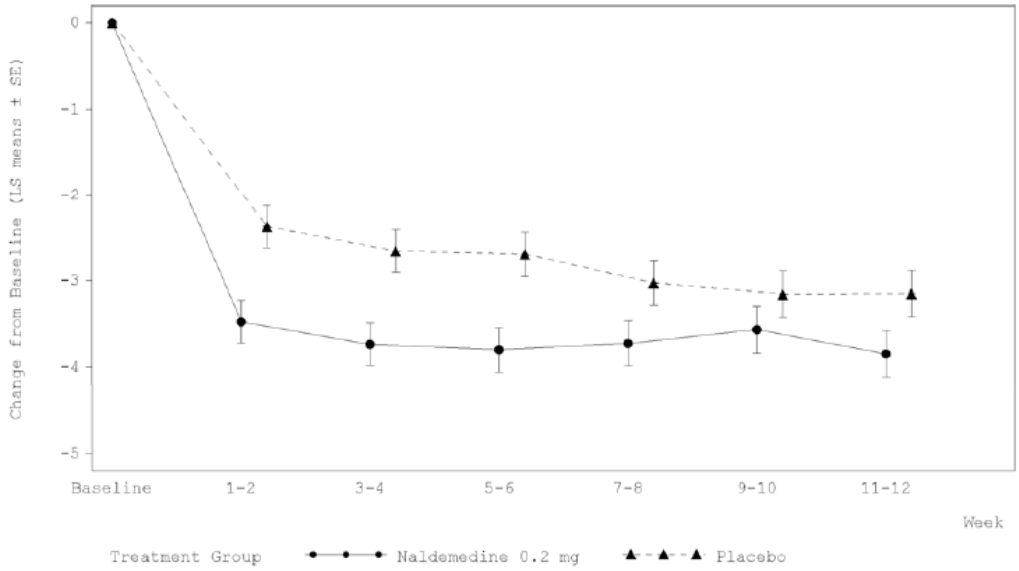
Figure 11-2 Kaplan-Meier Curve of Time to First Spontaneous Bowel Movement – Intent-to-Treat Population



The vertical line(|) represents censored time.
SBM = spontaneous bowel movement.

- Median time to first CSBM was 48.95 hours for the naldemedine group and 128.92 hours for the placebo, the difference being statistically significant.
- The proportion of subjects with SBM or CSBM within the first 4, 8, 12, 24, and 48 hours after initial dose of trial dug were higher for subjects on naldemedine compared to placebo.
- Change in maximal number of days between SBMs from baseline for each 2-week of the treatment period appeared higher for naldemedine than placebo for the first 2-weeks periods, but the difference decreased over time.

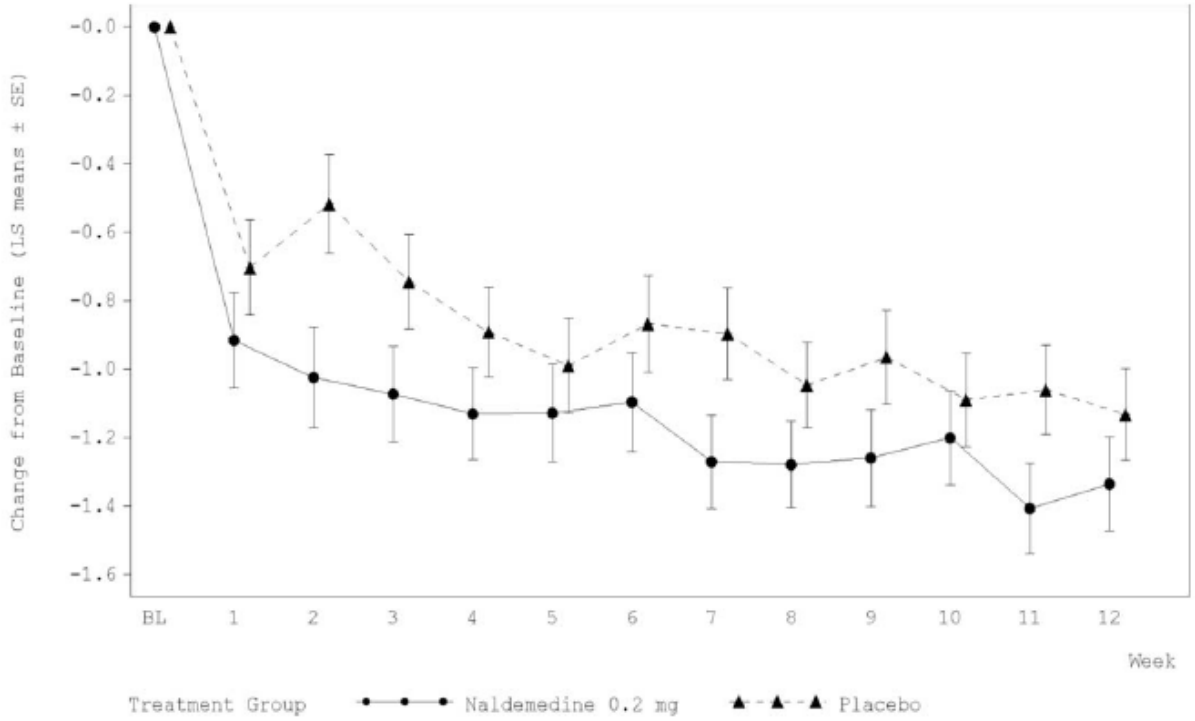
Figure 14.2-3.8 Change in Maximal Number of Days between SBMs from Baseline to Each Two Weeks (LS Mean ± SE)
ITT Population



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

- There was no difference in the change in the frequency of rescue laxative use per week from baseline to each week between the treatments, although at each week naldemedine was numerically higher. The same pattern was found for change in the number of days of rescue laxative use per week from baseline to each week.

Figure 11-3 **Change in the Frequency of Rescue Laxative Use per Week from Baseline to Each Week (Least-Squares Mean ±Standard Error) – Intent-to-Treat Population**



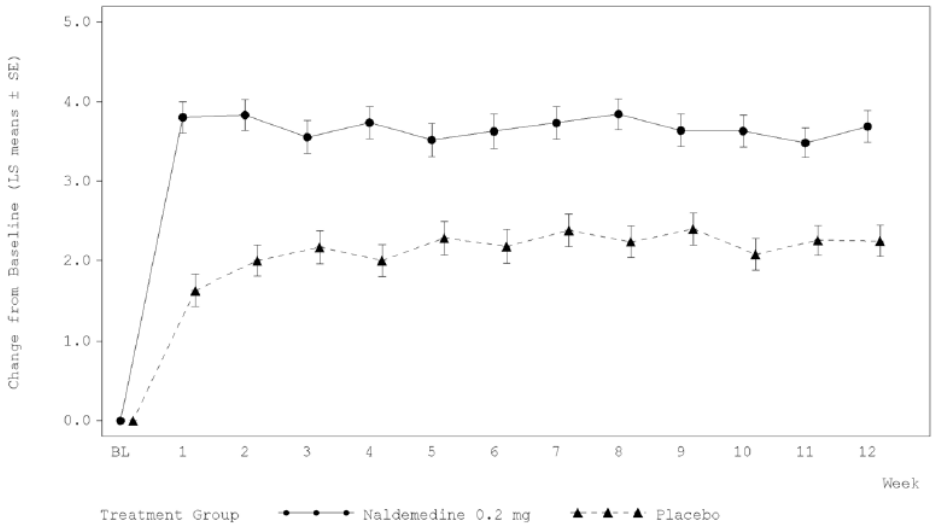
Baseline (BL) was 14 consecutive calendar day qualifying period during the Screening Period.
LS = least squares; SE = standard error.

- Abdominal bloating score and abdominal discomfort score decrease from baseline over the treatment period for both groups with generally similar reductions.
- Changes in the overall score for PAC-SYM from baseline to each visit were statistically significantly greater for naldemedine than placebo. Treatment effects of -0.29, -0.33, and -0.30 respectively.
    - The results for each domain of the PAC-SYM were generally similar to the overall score.
- Changes in the overall score for PAC-QOL from baseline to each visit were statistically significantly greater for naldemedine than placebo. Treatment effects of -0.30, -0.33, and -0.26 respectively.
    - The results for each domain of the PAC-QOL were generally similar to the overall score.
- Change overall and in each domain scores for SF-36 from baseline to Week 12/early termination were generally small and similar between groups.
- For the subjects who completed a Subject Global Satisfaction questionnaire, the degree of satisfaction of constipation and abdominal symptoms was more improved for naldemedine than for placebo.
- The changes in total and free testosterone in males from baseline to Week 12/early termination were small and appeared similar between groups (no statistical test performed).

V9232:

- For CSBM a responder was defined similar to a responder for SBM. The proportion of responders was 31.2% for naldemedine and 17.9% for placebo with a statistically significant difference between groups.
- When a responder was defined as a subject with at least **6** positive-response weeks out of the 12-week treatment period (with the usual definition of response-week), the proportion of responders was 68.8% for naldemedine and 47.1% for placebo with a statistically significant difference between groups.
- When a responder was defined as a subject with at least **9** positive-response weeks out of the 12-week treatment period (with the usual definition of response-week), the proportion of responders was 56.5% for naldemedine and 36.5% for placebo with a statistically significant difference between groups.
- When a responder was defined as a subject with at least **3** positive-response weeks out of the 4 weeks in a month (with the usual definition of response-week), the proportion of monthly responders for naldemedine and placebo were 64.0% and 40.2% for Month 1, 68.5% and 48.2% for Month 2, and 65.4% and 47.3% for Month 3. The difference between groups was statistically significant for all months.
- Changes over time in the frequency of SBMS per week from baseline increased at Week 1 more for naldemedine than for placebo, and this difference between groups first declined slightly and then remained stable throughout Week 12 with a statistically significant difference between groups at all time points. See the plot below.

Figure 11-1 **Change in the Frequency of Spontaneous Bowel Movements per Week from Baseline to Each Week (Least-Squares Mean ± Standard Error) – Intent-to-Treat Population**

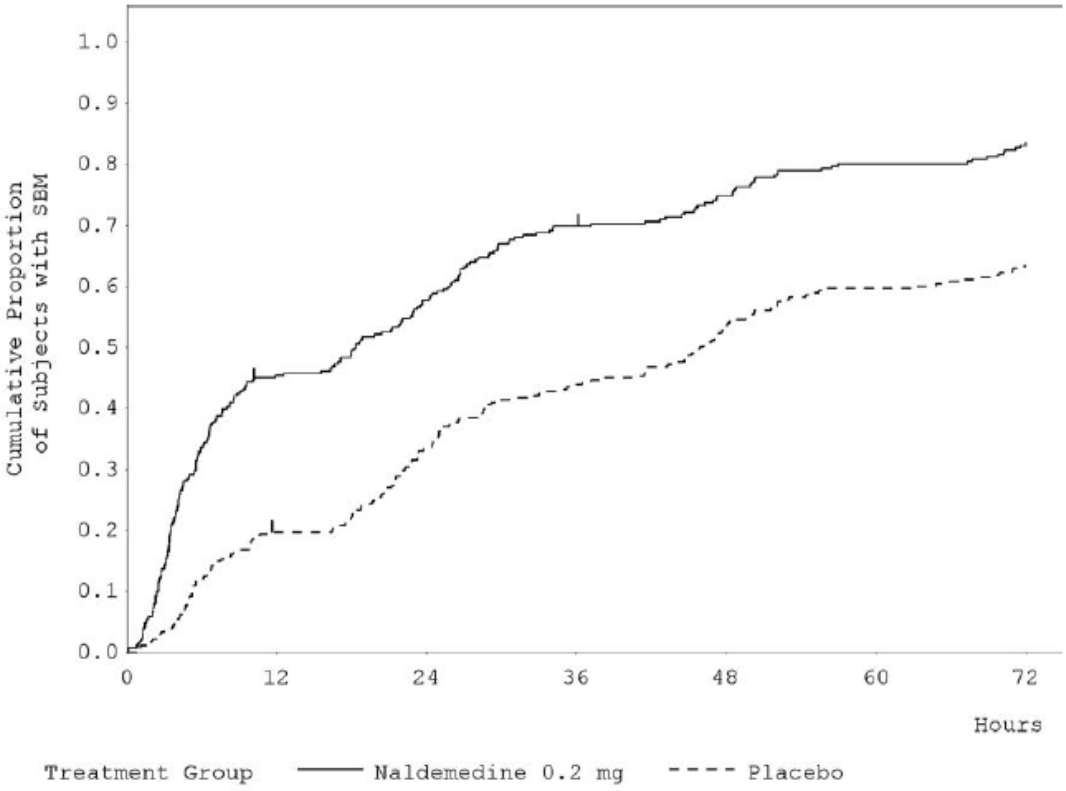


Baseline (BL) was 14 consecutive calendar day qualifying period during the Screening Period.

- Changes in the 6 other parameters: frequency of SBMs rated as 3 or 4 on the BSS per week, frequency of CSBMs per week, frequency of SBMs without straining per week, frequency of SBMs without blockage per week, number of days with at least 1 SBM per week, and number of days with at least 1 CSBM per week showed the same pattern as the results for change from baseline over time in the frequency of SBMs per week.

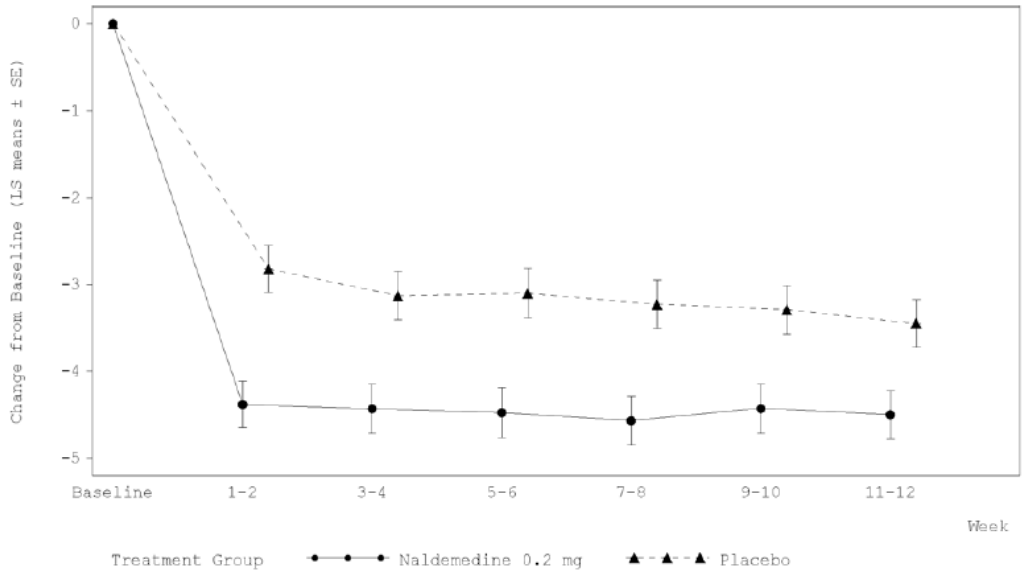
- Median time to first SBM was 18.33 hours for the naldemedine group and 45.92 hours for the placebo group, the difference being statistically significant. See the plot below.

Figure 11-2 Kaplan-Meier Curve of Time to First Spontaneous Bowel Movement – Intent-to-Treat Population



- Median time to first CSBM was 49.47 hours for the naldemedine group and 136.78 hours for the placebo group, the difference being statistically significant.
- The proportion of subjects with SBM or CSBM within the first 4, 8, 12, 24, and 48 hours after initial dose of trial dug were higher for subjects on naldemedine compared to placebo.
- Change in maximal number of days between SBMs from baseline for each 2-week of the treatment period appeared higher for naldemedine than placebo for the first 2-weeks period, with the difference being rather stable over time but maybe with a slight tendency to decrease.

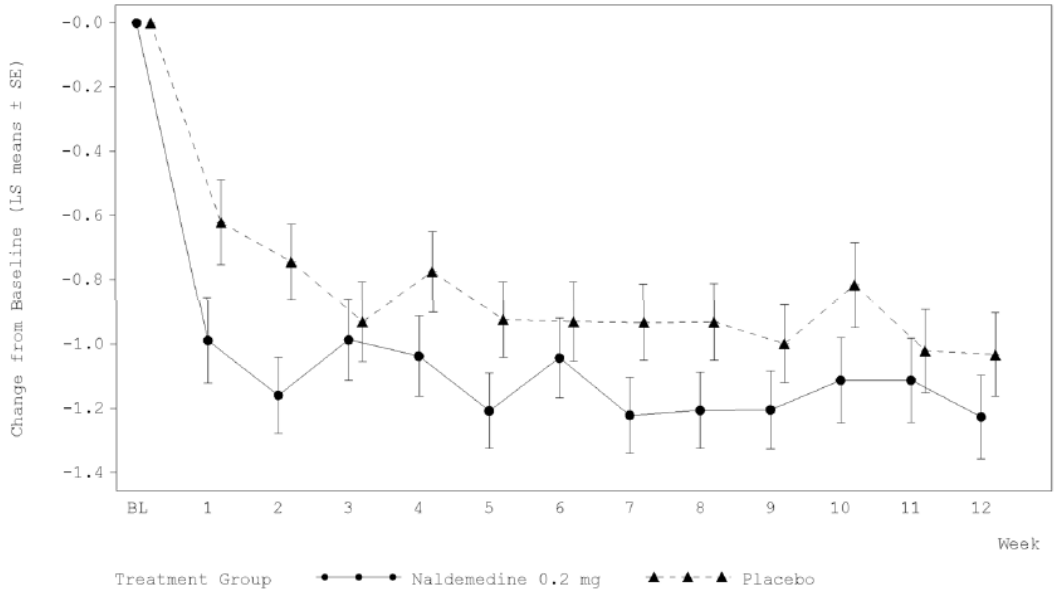
Figure 14.2-3.8 Change in Maximal Number of Days between SBMs from Baseline to Each Two Weeks (LS Mean ± SE)
ITT Population



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

- There was generally no difference in the change in the frequency of rescue laxative use per week from baseline to each week between the treatments, although at each week naldemedine was numerically higher. The same pattern was found for change in the number of days of rescue laxative use per week from baseline to each week.

Figure 11-3 **Change in the Frequency of Rescue Laxative Use per Week from Baseline to Each Week (Least-Squares Mean ± Standard Error) – Intent-to-Treat Population**



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

- Abdominal bloating score and abdominal discomfort score decrease from baseline over the treatment period for both groups with statistically higher reductions for the naldemedine group.
- Changes in the overall score for PAC-SYM from baseline to each visit were statistically significantly greater for naldemedine than placebo. Treatment effects of -0.29, -0.33, and -0.32 respectively.

    - The results for each domain of the PAC-SYM were generally similar to the overall score.
- Changes in the overall score for PAC-QOL from baseline to each visit were statistically significantly greater for naldemedine than placebo. Treatment effects of -0.29, -0.34, and -0.28 respectively.
    - The results for each domain of the PAC-QOL were generally similar to the overall score.
- Change overall and in each domain scores for SF-36 from baseline to Week 12/early termination were generally small and similar between groups.
- For the subjects who completed a Subject Global Satisfaction questionnaire, the degree of satisfaction of constipation and abdominal symptoms was more improved for naldemedine than for placebo.
- The changes in total and free testosterone in males from baseline to Week 12/early termination were small and appeared similar between groups (no statistical test performed).

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 16 Summary of Efficacy for Trial V9231

Title: A Randomized, Double-blind, Placebo-controlled, Parallel-group Study of Naldemedine in the Treatment of Opioid-induced Constipation in Subjects with Non-malignant Chronic Pain Receiving Opioid Therapy		
Study Identifier	1314V9231	
Design	Phase 3, randomised, double-blind, placebo-controlled, parallel-group study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks treatment and 4 weeks follow-up 14-28 days screening phase not applicable
Hypothesis	Superiority	
Treatment Groups	Naldemedine 0.2 mg	Naldemedine oral tablet 0.2 mg QD for 12 weeks, 274 patients randomised
	Placebo	Placebo QD for 12 weeks, 273 patients randomized

Endpoints and Definitions	Primary endpoint	Proportion of SBM responders	A responder was defined as a subject who had ≥ 9 positive-response weeks out of 12 weeks and ≥ 3 positive-response weeks out of the last 4 weeks. A positive-response week was defined as ≥ 3 SBMs/week and ≥ 1 SBM/week increase from baseline.
	Secondary endpoint	Change in frequency of SBM/week	Change from baseline in frequency of SBMs to the last 2 weeks of treatment.
	Secondary endpoint	Change in frequency of SBM/week	Change from baseline in frequency of SBMs from baseline to week 1.
	Secondary endpoint	Change in frequency of CSBM/week	Change from baseline in frequency of CSBMs to the last 2 weeks of treatment.
	Secondary endpoint	Change in frequency of SBM/week without straining	Change in frequency of SBMs without straining from baseline to the last 2 weeks of the treatment period.
Database Lock	26 February 2015		
Results and Analysis			
Analysis Description	**Primary Analysis**		
Analysis Population and Time Point Description	Intent-to-treat (all subjects randomised), results for various timepoints during the 12-week treatment period as detailed below		

Descriptive Statistics and Estimate Variability	Treatment group	Naldemedine 0.2 mg	Placebo
	Number of subjects	273	272
	SBM response rate over 12-weeks (%)	47.6 (130/273)	34.6 (94/272)
	95% CI	41.6, 53.7	28.9, 40.5

Effect Estimate Per Comparison	SBM response rate (%)	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	13.0
		95% CI for difference	4.8, 21.3
		P-value (Cochran-Mantel-Haenszel test)	0.0020

Notes	The 95% CI for the response rate in each treatment group was estimated by the Clopper-Pearson method. The difference in proportions was calculated by the estimator given by Koch et al. The P-value was calculated by Cochran-Mantel-Haenszel test adjusted by the opioid dose strata.		
Analysis Description	**Secondary Analysis**		
Descriptive Statistics and Estimate Variability	Treatment group	Naldemedine 0.2 mg	Placebo
	Number of subjects	273	272
	Change in SBM/week in last 2 weeks (LS mean)	3.42	2.12
	SE	0.193	0.192
	Change in SBM/week to week 1 (LS mean)	3.48	1.36
	SE	0.185	0.184
	Change in CSBM/week in last 2 weeks (LS mean)	2.58	1.57
	SE	0.170	0.170
	Change in SBM/week without straining in last 2 weeks (LS mean)	1.46	0.73
	SE	0.141	0.140

Effect Estimate Per Comparison	Change in SBM/week in last 2 weeks (LS mean)	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	1.30
		95% CI for difference	0.77, 1.83
		P-value (ANCOVA)	<0.0001
	Change in SBM/week to week 1 (LS mean)	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	2.11
		95% CI for difference	1.60, 2.63
		P-value (ANCOVA)	<0.0001
	Change in CSBM/week in last 2 weeks (LS mean)	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	1.01
		95% CI for difference	0.54, 1.48

		P-value (ANCOVA)	<0.0001
	Change in SBM/week without straining in last 2 weeks (LS mean)	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	0.73
		95% CI for difference	0.34, 1.12
		P-value (ANCOVA)	0.0003
Notes	The ANCOVA model has the terms for treatment group as a fixed effect and the opioid dose strata as a covariate. The primary and the 4 secondary endpoints were tested in a predefined hierarchical order		
Abbreviations/Definitions	ANCOVA=analysis of covariance; BM=bowel movement; CI=confidence interval; CSBM=complete spontaneous bowel movement; QD=once daily; SBM=spontaneous bowel movement (A BM occurring within 24 hours after rescue laxative therapy was not considered an SBM)		

Table 17 Summary of Efficacy for Trial V9232

Title: A Randomized, Double-blind, Placebo-controlled, Parallel-group Study of Naldemedine in the Treatment of Opioid-induced Constipation in Subjects with Non-malignant Chronic Pain Receiving Opioid Therapy			
Study Identifier	1315V9232		
Design	Phase 3, randomised, double-blind, placebo-controlled, parallel-group study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks treatment and 4 weeks follow-up 14-28 days screening phase not applicable
Hypothesis	Superiority		
Treatment Groups	Naldemedine 0.2 mg		Naldemedine oral tablet 0.2 mg QD for 12 weeks, 277 patients randomised
	Placebo		Placebo QD for 12 weeks, 276 patients randomized
Endpoints and Definitions	Primary endpoint	Proportion of SBM responders	A responder was defined as a subject who had ≥ 9 positive-response weeks out of 12 weeks and ≥ 3 positive-response weeks out of the last 4 weeks. A positive-response week was defined as ≥ 3 SBM/week and ≥ 1 SBM/week increase from baseline.

	Secondary endpoint	Change in frequency of SBM/week	Change from baseline in frequency of SBMs to the last 2 weeks of treatment.
	Secondary endpoint	Change in frequency of SBM/week	Change from baseline in frequency of SBMs from baseline to week 1.
	Secondary endpoint	Change in frequency of CSBM/week	Change from baseline in frequency of CSBMs to the last 2 weeks of treatment.
	Secondary endpoint	Change in frequency of SBM/week without straining	Change in frequency of SBMs without straining from baseline to the last 2 weeks of the treatment period.

Database Lock	16 July 2015			
Results and Analysis				
Analysis Description	**Primary Analysis**			
Analysis Population and Time Point Description	Intent-to-treat (all subjects randomised), results for various timepoints during the 12-week treatment period as detailed below			
Descriptive Statistics and Estimate Variability	Treatment group		Naldemedine 0.2 mg	Placebo
	Number of subjects		276	274
	SBM response rate over 12-weeks (%)		52.5 % (145/276)	33.6 % (92/274)
	95% CI		46.5, 58.6	28.0, 39.5
Effect Estimate Per Comparison	SBM response rate (%)	Comparison groups		Naldemedine 0.2 mg vs placebo
		Difference in proportions		18.9
		95% CI for difference		10.8, 27.0
		P-value (Cochran-Mantel-Haenszel test)		< 0.0001
Notes	The 95% CI for the response rate in each treatment group was estimated by the Clopper-Pearson method. The difference in proportions was calculated by the estimator given by Koch et al. The P-value was calculated by Cochran-Mantel-Haenszel test adjusted by the opioid dose strata.			

Analysis Description	**Secondary Analysis**		
Descriptive Statistics and Estimate Variability	Treatment group	Naldemedine 0.2 mg	Placebo
	Number of subjects	276	274
	Change in SBM/week in last 2 weeks (LS mean)	3.56	2.16
	SE	0.174	0.174
	Change in SBM/week to week 1 (LS mean)	3.86	1.69
	SE	0.199	0.198
	Change in CSBM/week in last 2 weeks (LS mean)	2.77	1.62
	SE	0.166	0.166
	Change in SBM/week without straining in last 2 weeks (LS mean)	1.85	1.10
	SE	0.163	0.162

Effect Estimate Per Comparison	Change in SBM/week in last 2 weeks (LS mean)	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	1.40
		95% CI for difference	0.92, 1.88
		P-value (ANCOVA)	< 0.0001
	Change in SBM/week to week 1 (LS mean)	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	2.17
		95% CI for difference	1.63, 2.71
		P-value (ANCOVA)	<0.0001
	Change in CSBM/week in last 2 weeks (LS mean)	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	1.15
		95% CI for difference	0.70, 1.61
		P-value (ANCOVA)	<0.0001
	Change in SBM/week without straining in last 2	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	0.75

	weeks (LS mean)	95% CI for difference	0.30, 1.19
		P-value (ANCOVA)	0.0011
Notes	The ANCOVA model has the terms for treatment group as a fixed effect and the opioid dose strata as a covariate. The primary and the 4 secondary endpoints were tested in a predefined hierarchical order		
Abbreviations/Definitions	ANCOVA=analysis of covariance; BM=bowel movement; CI=confidence interval; CSBM=complete spontaneous bowel movement; QD=once daily; SBM=spontaneous bowel movement (A BM occurring within 24 hours after rescue laxative therapy was not considered an SBM)		

Trial V9235

Trial V9235 is entitled "A randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3 study to evaluate the long-term safety of naldemedine for the treatment of opioid-induced constipation in subjects with non-malignant chronic pain receiving opioid therapy".

The trial was a randomized, double-blind, placebo-controlled, parallel-group, multicentre, multinational trial comparing safety of naldemedine 0.2 mg QD versus placebo. The trial consisted of a 14-28-day screening period, a 52-week treatment period, and a 2-week follow-up period.

At visit 1 subjects were screened to determine eligibility. Subjects provided the investigator with details of their laxative regimen for the previous 28 days. This regimen was used throughout the screening period. At visit 2, up to 28 days later, subjects were randomized to treatment with either naldemedine or placebo for 12 weeks.

During the treatment period subjects attended 12 scheduled visits: baseline/randomization, Week 1, Week 2, Week 6, Week 12, Week 18, Week 24, Week 30, Week 26, Week 42, Week 48, and Week 52, and completed the Bowel Habits paper diary for the weeks prior to Week 12, Week, 24, and Week 52. The PAC-SYM/PAC-QOL was completed at selected scheduled treatment visits whereas Subject Global Satisfaction was completed at end of treatment period.

Methods

Study Participants

The trial was conducted in patients with chronic non-cancer pain and OIC and investigated the effect of naldemedine relative to placebo. Subjects on a stable laxative regimen at screening should continue on that regimen throughout the study.

The main inclusion criteria were

- 18-80 years of age, inclusive
- Diagnosis of chronic non-cancer pain and OIC
- Receiving chronic opioid therapy for at least 3 months

    - Opioid regimen stable at a TDD on average of at least 30 mg equivalents of oral morphine sulphate for at least 1 months prior to screening (tramadol and tapentadol not included in calculations, with no anticipated changes in the overall opioid regimen)

- Patients must have met the following 3 criteria over a 14-consecutive-day qualifying period during the screening period:
    - No more than 4 SBMs during the 14-consecutive-day qualifying period, and no more than 3 SBMS in a given week of the qualifying period
    - Recordance of at least 4 days of bowel movement data for each 7 day period that constitutes one week in the eDiary.
- Subjects may or may not have been on a routine laxative regimen at screening. Subjects on a laxative regimen must have been taking laxatives at least once weekly.

Trial drug was to be discontinued for any of the following reasons:

- Withdrawal by subject
- On the discretion of the investigator because of safety reasons
- If the subject met the liver discontinuation criteria (abnormal liver chemistry criteria)
- Lost to follow-up
- Pregnancy
- Any protocol deviation that resulted in a significant risk to the subject's safety
- Unblinding

Withdrawal from the trial: subjects may voluntarily withdraw from the trial for any reason at any time. For withdrawn subjects every effort is made to complete the end-of-study assessments. All subjects who withdrew or discontinued were to be followed until resolution of any adverse events or until the unresolved adverse events were judged by the investigator to have stabilised.

Treatments

Patients were randomized 1:1 to receive either naldemedine 0.2 mg QD or placebo tables matching 0.2 mg naldemedine QD orally. Patients were instructed to choose the most appropriate time for daily dosing (i.e. the time associated with the highest compliance and convenience relative to occurrence of BMs) and to take the drug at approximately the same time each day.

Opioid treatment: The stable opioid treatment regimen at a TDD on average of at least 30 mg equivalents of oral morphine sulphate at screening was to be continued throughout the study. Patients were allowed to take additional medication (opioid or non-opioid) for breakthrough pain as prescribed by their physician.

Rescue medication: If a subject did not have BM for any 72 hours period during screening or treatment a rescue laxative different from the subjects' regular regimen was allowed and had to be documented in the eDiary. Study drug was continued throughout the study despite whether rescue medication was taken or not. A BM occurring within 24 hours after rescue therapy was not counted as an SBM.

Objectives

Primary objective: To assess the overall safety and tolerability during 52 weeks of treatment with naldemedine 0.2 mg QD in subjects with chronic non-cancer pain OIC.

Secondary objectives: To assess the effect of naldemedine 0.2 mg QD on quality of life measures, global satisfaction, opiate withdrawal, pain intensity, OID symptoms and laxative use.

Outcomes/endpoints

The primary objective was overall assessment of safety, hence assessments of summary measures of treatment emergent adverse events was the primary endpoint.

Additional safety endpoints were:

- Incidence of TEAEs
- SAES
- AEs leading to discontinuation

MACE, COWS/SOWS, the 11-point NRS for pain intensity, and the standard safety evaluations.

The secondary efficacy endpoints were:

- Change in the frequency of BMs from baseline to selected time points (Week 12, 24, 36, and 52) of the treatment period
- Number of subjects with laxative use
- Change in the PAC-SYM/PAC-QOL overall score from baseline to each visit
- Frequency of Subject Global Satisfaction by treatment group

Exploratory endpoint:

- Change in total and free testosterone in males

Note that no formal statistical test was defined for the primary endpoint and that no multiplicity adjustment was performed for the secondary endpoints.

Sample size

Approximately 1200 subjects were to be randomized 1:1 to the naldemedine 0.2 mg group respectively the placebo group in order to meet or exceed the requirements of the ICH E1 Guideline: The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions, i.e. 6 months of exposure for 300-600 subjects as well as 1 year of exposure for 100 subjects.

Randomisation

At visit 2, eligible patients were randomised in a 1:1 manner to one of the treatment groups using a telephone or web-based randomisation system, IXRS. Patients were stratified based on their documented opioid use (average TDD during the 14-consecutive-day qualifying period) (30 to at most 100mg equivalents of oral morphine sulphate, or more than 100 mg equivalents of oral morphine sulphate).

Blinding (masking)

The trial was a double-blind placebo-controlled trial. Placebo tablets were identical to active tablets in shape and colour.

All subjects, study personnel, and data analysts were blinded to the treatment assigned at randomization until database lock. The randomization schedule was only accessible to Drug Supply Management staff, IXRS Clinical coordinators/vendor staff, and unblinded statistician on the Data Safety Monitoring Board.

Statistical methods

Primary endpoint: Assessments of summary measures of treatment emergent adverse events.

Analysis populations:

ITT: All randomized subjects. Analysed as randomised.

Safety population: All randomised subjects who received at least one dose of trial drug will be analysed by treatment actually received. Subjects who took naldemedine at least once will be analysed by the naldemedine group.

Statistical analysis of primary endpoint: Summary measures of treatment emergent adverse events were assessed for the safety population.

Secondary efficacy endpoints:

The frequency of BMs per week for each selected visit was defined as 7*(total frequency of BMs for each selected visit)/(Number of days of observation related to defecation for each selected visit), i.e. it is the observed average scaled to a 7-day observation period.

The change in the frequency of BMs per week from baseline to each selected visit was defined as (Frequency of BMs per week for selected visit)-(Frequency of BMs per week in baseline period).

The mean (overall) scores for the PAC-SYM/PAC-QOL for each visit were defined as (Total score of the PAC-SYM/PAC-QOL for each visit)/(Number of items entered for each visit) and the domain scores were defined similarly.

Statistical analysis of secondary endpoints:

- Analysis of changes in frequency of BMs from baseline to selected time points of the treatment period as well as analysis of changes in the mean (overall or domain) scores for PAC-SYM/PAC-QOL will be done using MMRM including opioid group strata, treatment group, time, and time-by-treatment group interaction as fixed factors. An unstructured covariance matrix within subjects will be assumed.
- Frequencies of Subject Global Satisfaction were summarized by treatment and compared between groups using the Wilcoxon rank sum test.
- The proportion of subjects meeting 3 different criteria for laxative use will be summarised by treatment group.

The population will be the ITT population consisting of all randomized subjects for all efficacy analyses.

Statistical analysis of exploratory endpoints:

Summary statistics for total and free testosterone in males will be calculated by treatment group.

Subgroup analyses:

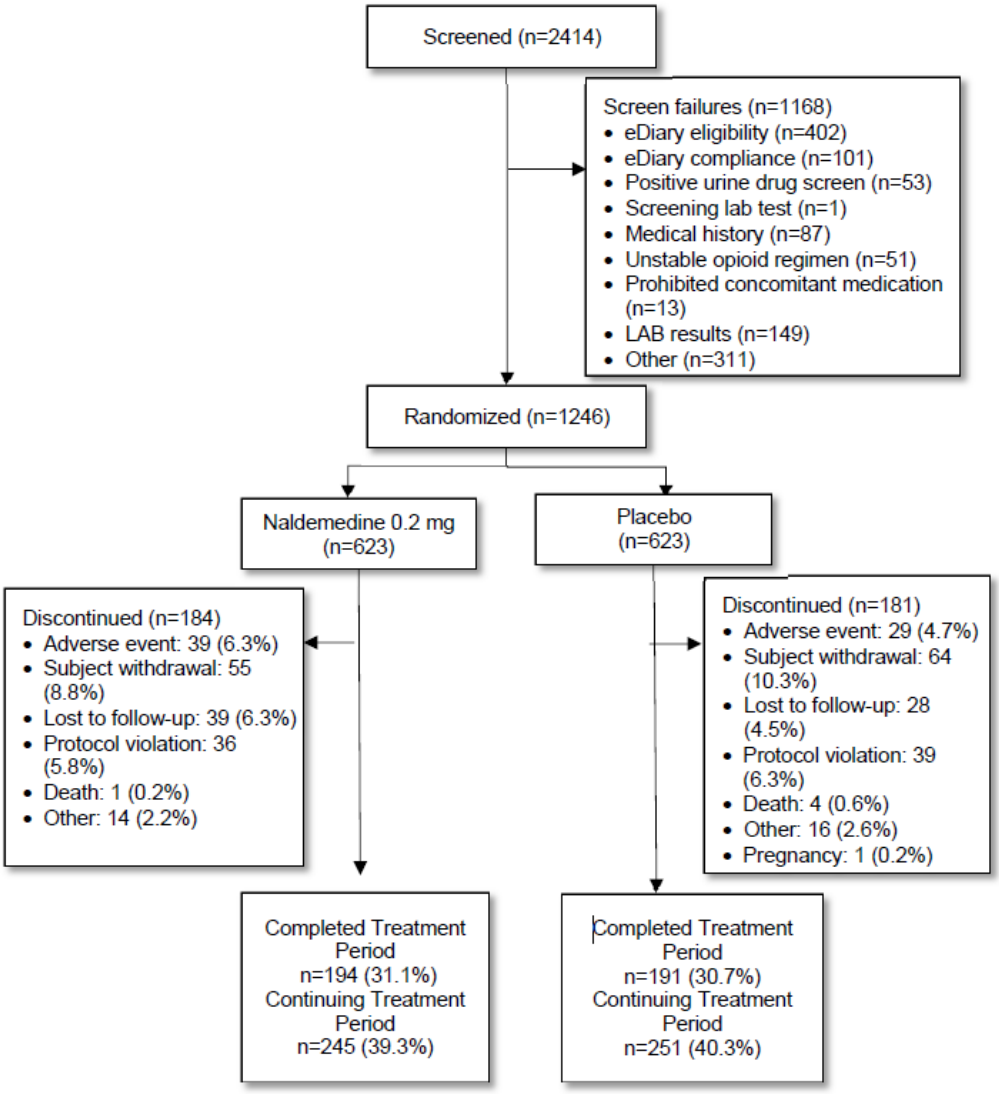
In addition the secondary efficacy endpoints change in frequency of BMs per week, and change in overall and domain scores of PAC-SYM/PQC-QOL were analysed for the following subgroups:

- **Subjects not on a stable laxative regimen** defined as subject who did not have a laxative from the 28 days prior to the screening period to the final dose of study drug or who received only rescue laxative (any laxatives that subjects started to take during the treatment period) (criteria 1).
- **Subjects on a stable laxative regimen** defined as subjects who have at least one stable laxative use reported from 28 days prior to screening to the final dose of study drug (criteria 2).

Results

Participant flow

A total of 2414 subjects were screened. Out of these 1168 (48%) failed screening mainly due to eDiary eligibility and Other, resulting in a total of 1246 subjects randomised, 623 to naldemedine and 623 to placebo. At this point in time 194 (31.1%) and 191 (30.7%) have completed the treatment period with 245 (39.3%) and 251 (40.3%) still continuing the treatment period for naldemedine and placebo, i.e. similar proportions in the two groups. Subject withdrawal was the main reason for discontinuation followed by adverse events. Subject withdrawal appeared slightly more common for subjects on placebo (10.3% compared to 8.8%) while adverse events appeared slightly more common for subjects on naldemedine (6.3% compared to 4.7%). In the naldemedine group 23 (3.7%) subjects withdrew due to AEs in the gastrointestinal disorders SOC, compared to 7 (1.1%) subjects in the placebo group. Apart from this reasons for withdrawal seemed balanced and completion rates so far comparable.



Recruitment

The trial was a multicentre trial with 195 trial sites in 14 countries (Australia, Belgium, Canada, Denmark, Estonia, France, Germany, Hungary, Poland, South Africa, Spain, Sweden, United Kingdom, and the US). The first subject was enrolled in September 2013 and the data cut-off date was 24 June 2015.

Conduct of the study

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice.

There were 3 amendments to the protocol. The original protocol dated 09 July 2013 was amended on 07 October 2013 (Amendment 1), 16 June 2014 (Amendment 2), and 26 February 2015 (Amendment 3). The key changes in amendment 1 were addition of pregnancy test at Visit 2, added directions for collecting data for laxative use, recording of opioid pain medications, that opioid therapy should be captured on the CRF throughout the study, added list of prohibited medications during the study. Key changes in amendment 2 were the extra inclusion criteria “No more than 4 SBMs during the 14-consecutive-day qualifying period, and no more than 3 SBMS in a given week of the qualifying period”, added text to specify that subjects might use laxatives during the screening period, added text to specify

that tramadol and tapentadol would not be used in the calculations for the stable opioid treatment regimen, and were only allowed in conjunction with other opioid agonists, and added change in frequency of BMs from baseline to select time point as an efficacy endpoint. Key changes in amendment 3 was change in the wording of the primary objective, change of the sample size per agreement with the US FDA and per alignment with ICH Guidance E1, added text about Core Period Data Set and Supplemental Period data set, changes to the formulation of blinding and unblinding, change of the primary endpoint from MACE to the incidence of TEAEs, SAEs, and AEs leading to discontinuation, early termination was changed to specify that subjects who terminated early should also have a follow-up period visit 2 weeks after their last dose of study drug, addition of adverse events of special interest. Rizmoic was chosen for a routine GCP inspection. At the inspection, critical GCP violations were recorded for study V9235 necessitating exclusion of data from these sites. The overall results were not significantly affected by the exclusion of data. In addition, it was noted that patients did not have the possibility to correct the electronic diary regarding the number of spontaneous bowl movements. This was considered a critical GCP finding. The applicant was therefore requested to complete and submit a re-analysis of efficacy data (of studies V9231, V9232 and V9235) including primary as well as secondary efficacy endpoint following correction of data based on the available source documentation at participating sites (including un-submitted and un-generated DCFs).

Baseline data

The demographic characteristics of the safety population were generally well balanced across treatment groups. The mean age was 53 years with 74.2% of subjects being between 40 and 65 years, and 14.3% above 65 years. The majority of patients were female (63.3%) and predominantly White (79.7%) followed by Black/African American subjects (18.4%). The subjects were mainly from North America (86.5%). The study population had a mean weight of 90.45 kg, and the majority of subjects (83.7%) were overweight or obese (BMI above 25 kg/m2). At baseline, the mean total daily dose of the opioid analgesic was 123.0 mg morphine-equivalent for the naldemedine group and 121.1 mg morphine-equivalent for the placebo group. A total of 21 subjects equally split between groups were randomised although their average TDD was less than stated in the inclusion criteria. The majority of subjects (63.5%) were in the low opioid dose strata. The mean SBMs per week was 1.60 with a median of 1.59.

Table 10-2 Spontaneous Bowel Movements per Week at Baseline – Safety Population

	Naldemedine 0.2 mg N=621	Placebo N=619	Total N=1240
n	621	619	1240
Mean	1.59	1.62	1.60
SD	0.665	0.616	0.641
Min	0.0	0.0	0.0
Median	1.56	1.62	1.59
Max	7.5	4.4	7.5
	n (%)	n (%)	n (%)
<1	73 (11.8)	64 (10.3)	137 (11.0)
>=1 to <2	304 (49.0)	288 (46.5)	592 (47.7)
>=2 to <3	237 (38.2)	262 (42.3)	499 (40.2)
>=3	7 (1.1)	5 (0.8)	12 (1.0)

Note that 12 subjects had more than 3 SBMS per week at baseline as this was calculated as (total number of SBMS/number of observation days) for the 14-consecutive-day qualifying period. For 10 subjects this was because that during the 14-day period they had a total of 4 SBMs and entered SBM data for 8 or 9

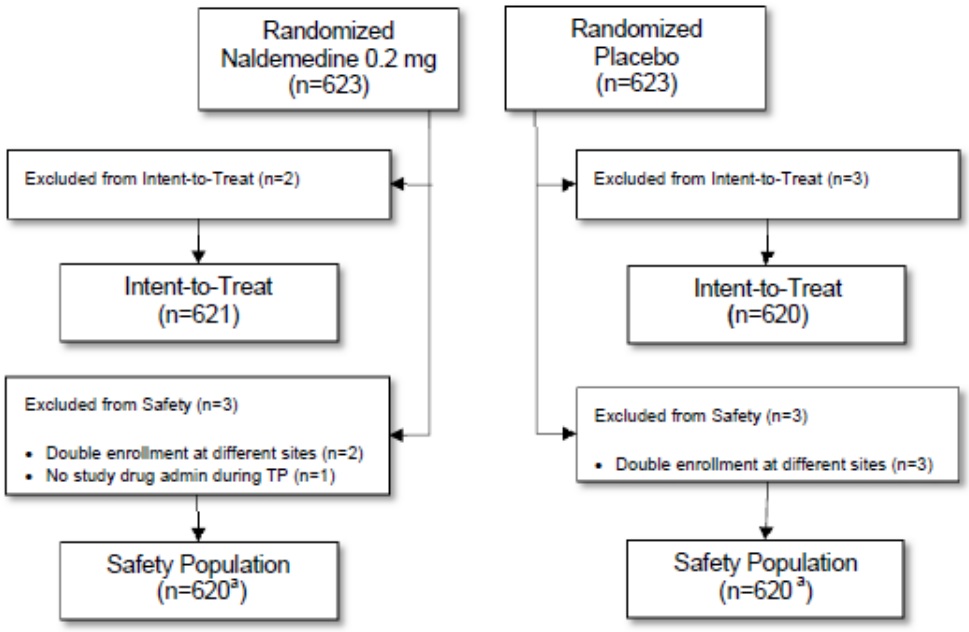
days, but still satisfied the inclusion criteria. The last 2 subjects, one in each group, had more than 4 SBMS during the 14-day-qualifying period and were randomised in error.

All subjects in the ITT population had a non-malignant chronic pain condition requiring treatment with opioids, and all subjects also had constipation, apart from one subject in the naldemedine group. This subject did not have constipation reported in medical history, but did meet the bowel movement entry criteria. The most commonly reported chronic pain conditions were back pain (58.6%), pain (6.7%), arthralgia (7.1%), neck pain (8.1%), osteoarthritis (9.5%), and fibromyalgia (5.3%). The most common reported medical history condition were back pain (66.0%), hypertension (49.0%), depression (41.5%), anxiety (34.7%), gastrooesophageal reflux disease (33.3%), osteoarthritis (9.5%), and insomnia (33.4%).

Numbers analysed

A total of 1246 subjects were randomised, 723 to each group. A total of 5 subjects were excluded from all populations as each was simultaneously enrolled at 2 different study sites. All other subjects were included in the ITT population. For the Safety Population one additional subject in the naldemedine group was excluded as study drug was never administered.

Note that one subject was randomized to placebo but received one or more tablets of naldemedine by error and therefore is counted in the naldemedine safety population. Thus the safety populations consisted of 621 subjects in the naldemedine group, and 619 in the placebo group.



Note: the excluded total in any population may not equal the total of the reasons for exclusion in that population due to subjects being counted in multiple categories.

TP, treatment period.

a Subject 52354-024, randomized to the placebo group, received one or more tablets of naldemedine by error. For all safety analysis this subject will be counted in the naldemedine group.

Outcomes and estimation

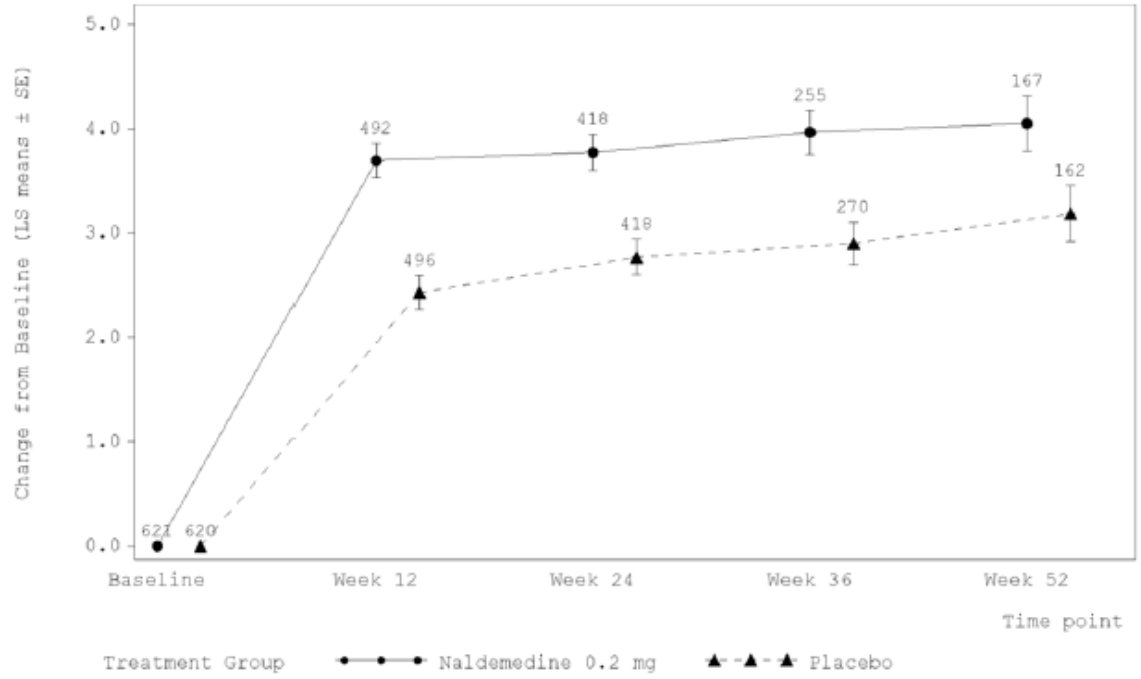
Primary analysis:

See the safety section.

Secondary efficacy endpoints:

- A greater change in the frequency of BMs per week from Baseline to Week 12 was found for naldemedine compared to placebo, treatment difference of 1.26 BMs per week ($p<0.0001$). This difference was sustained through Week 52, and significant at all time points.

Figure 11-1 **Change in the Frequency of Bowel Movements per Week from Baseline to Each Visit Assessed (Least-Squares Mean ± Standard Error) – Intent-to-Treat Population**



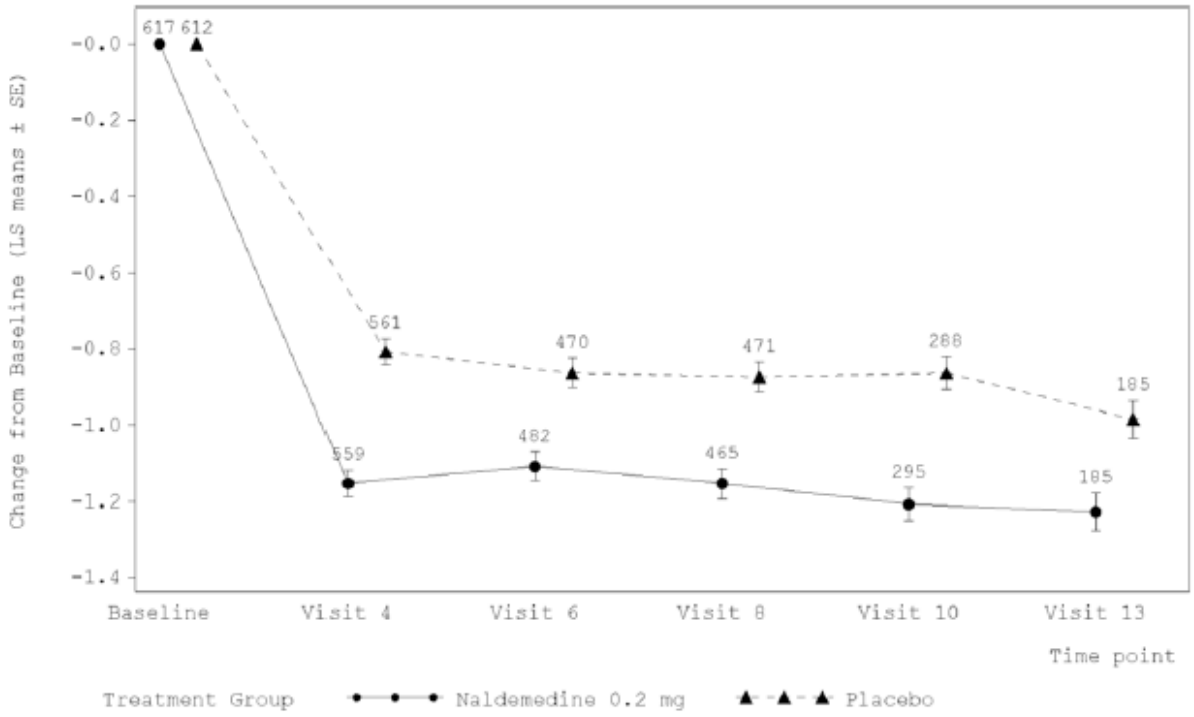
Baseline was 14 consecutive calendar day qualifying period during the Screening Period.

Frequency of BMs per week was calculated as the weekly average of observations in 7 days prior to each visit.

Number of subjects at each visit is shown in the figure.

- Subjects in the naldemedine group had a greater improvement from baseline in the mean overall PAC-SYM score over time than subjects in the placebo group with treatment effects varying from -0.24 to -0.35. The results were generally similar for each of the domain scores.

Figure 11-4 **Change in the Overall Score for Patient Assessment of Constipation Symptoms from Baseline to Each Visit Assessed (Least-Squares Mean ± Standard Error) – Intent-to-Treat Population**



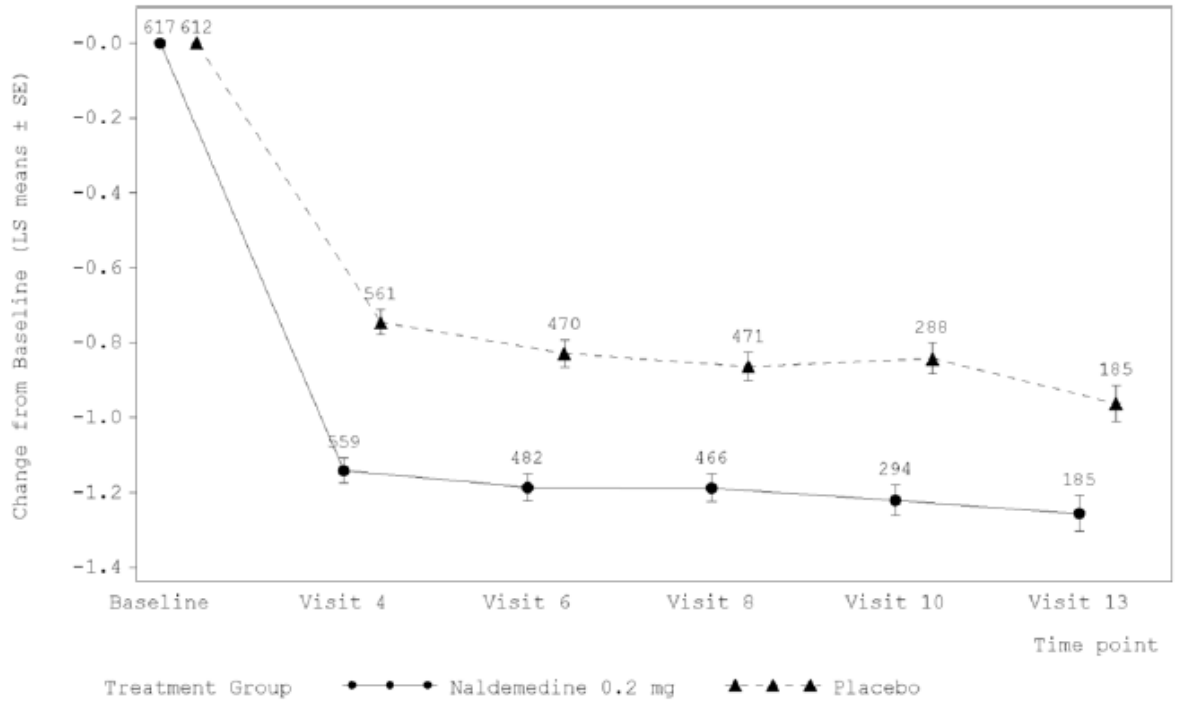
Baseline was Visit 2.

Visit 2 (Day 1), Visit 4 (Week 2), Visit 6 (Week 12), Visit 8 (Week 24), Visit 10 (Week 36), Visit 13 (Week 52).

Number of subjects at each visit is shown in the figure.

- Subjects in the naldemedine group had a greater improvement from baseline in the mean overall PAC-SYM score over time than subjects in the placebo group with treatment effects varying from -0.29 to -0.40. The results were generally similar for each of the domain scores.

Figure 11-8 **Change in the Patient Assessment of Constipation Quality of Life Overall Score from Baseline to Each Visit Assessed (Least-Squares Mean ± Standard Error) – Intent-to-Treat Population**



Baseline was Visit 2.

Visit 2 (Day 1), Visit 4 (Week 2), Visit 6 (Week 12), Visit 8 (Week 24), Visit 10 (Week 36), Visit 13 (Week 52).

Number of subjects at each visit is shown in the figure.

- **Subjects not on a stable laxative regimen** were defined as subject who did not have a laxative from the 28 days prior to the screening period to the final dose of study drug or who received only rescue laxative (any laxatives that subjects started to take during the treatment period) (criteria 1), whereas **Subjects on a stable laxative regimen** were defined as subjects who have at least one stable laxative use reported from 28 days prior to screening to the final dose of study drug (criteria 2).

About half of the subjects were on stable laxatives, 50.6% in the naldemedine group, and 54.2% in the placebo group. Out of these 7.3% respectively 12.2% received rescue laxatives. The proportion not on stable laxatives were about 30% in both groups, with respectively 6.5% and 12.0% receiving rescue laxatives. Close to 20% of subjects could not be classified as either on stable laxatives or not and are therefore not part of the subgroup analysis.

Table 11-1 **Number of Subjects Meeting Each Criterion of Laxative Use Reported from 28 Days Prior to Screening to Last Dose of Study Drug – Intent-to-Treat Population**

	Naldemedine 0.2 mg N=621 n (%)	Placebo N=620 n (%)
Subjects not on stable laxatives [a]	186 (30.0)	184 (29.7)
- Subjects who received rescue laxative [b]	12 (6.5)	22 (12.0)
Subjects on stable laxatives [c]	314 (50.6)	336 (54.2)
- Subjects who received rescue laxative [d]	23 (7.3)	41 (12.2)
Other subjects	121 (19.5)	100 (16.1)

Rescue was defined as any laxative taken for the first time during Treatment Period.

[a] Subject not on stable laxatives was defined as subject who did not have laxative use reported or received only rescue.

[b] The denominator is the number of subjects in [a].

[c] Subject on stable laxatives was defined as subject who might have at least one/any stable laxative use reported

[d] The denominator is the number of subjects in [c].

- Of the subjects who had completed the subject global satisfaction evaluation at end of study or early termination, 80.4% of subjects in the naldemedine group were moderately or more satisfied compared to 57.0% in the placebo group. The difference between groups were statistically significant.

Table 14.2-1.4 Analysis of Subject Global Satisfaction at Visit 13/Early Termination
ITT Population

Category	Naldemedine 0.2 mg N=621 n (%)	Placebo N=620 n (%)	P-value (Nominal)
MARKEDLY WORSENED	9 (3.2)	6 (2.1)	<.0001
MODERATELY WORSENED	3 (1.1)	9 (3.1)	
SLIGHTLY WORSENED	4 (1.4)	7 (2.4)	
UNCHANGED	40 (14.0)	103 (35.4)	
SLIGHTLY IMPROVED	49 (17.2)	66 (22.7)	
MODERATELY IMPROVED	85 (29.8)	48 (16.5)	
MARKEDLY IMPROVED	95 (33.3)	52 (17.9)	
Total	285 (100.0)	291 (100.0)	

Visit 13 (Week 52).
P-value was calculated by Wilcoxon rank sum test.

Exploratory efficacy evaluation:

The changes in total and free testosterone in males from baseline over time were small and similar between groups.

Subgroup analysis:

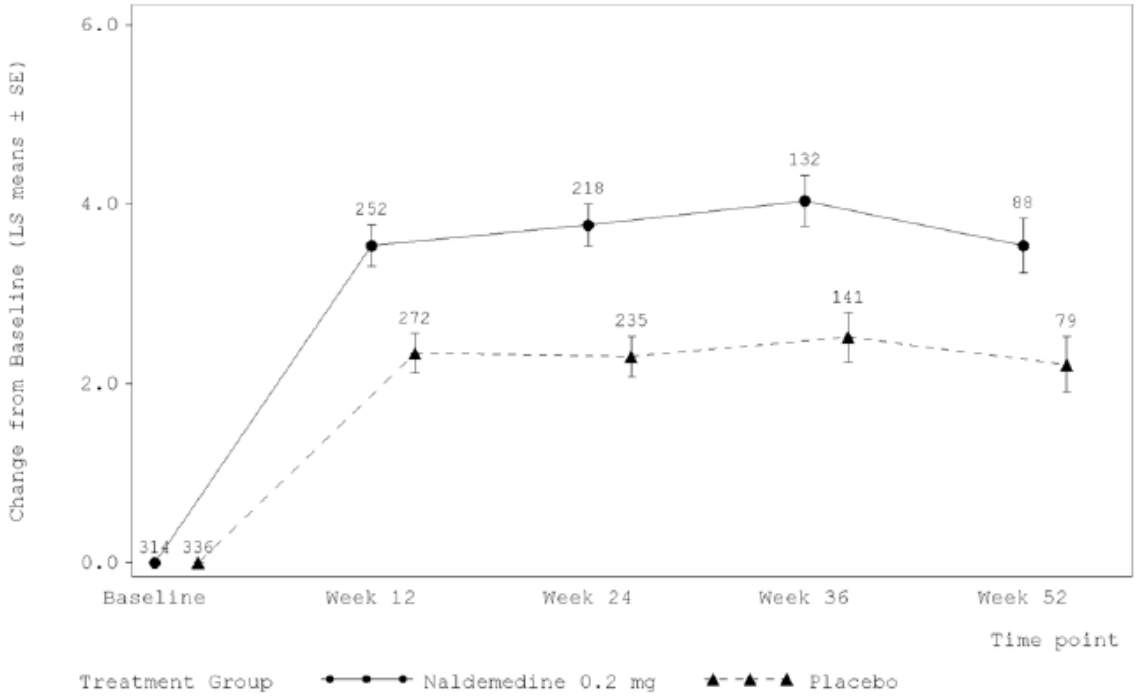
In addition the secondary efficacy endpoints were analysed for the subgroup *subjects on or not on a stable laxative regimen*. Note that the subgroup subjects on a stable laxative regimen is more than 50% larger than the subgroup of subjects not on a stable laxative regimen giving it a higher power for statistical comparisons. Also note that due to the nature of the data-cut, the number of subjects available for analysis after Week 24 diminishes with time.

Change in frequency of BMs:

- For subjects on a stable laxative regimen, a greater change in the frequency of BMs per week from Baseline to Week 12 was found for naldemedine compared to placebo, treatment difference of 1.20 BMs per week (p=0.0002). This difference was sustained through Week 52, and significant at all time points.

- For subject not on a stable laxative regimen, there was a greater change in the frequency of BMs per week from Baseline to Week 12 for naldemedine compared to placebo, treatment difference of 1.47 BMs per week (p=0.0006). But at subsequent visits there was no difference. The placebo response in this group was larger than the placebo response for subjects on a stable laxative regimen.

Figure 11-2 **Change in the Frequency of Bowel Movements per Week from Baseline to Each Visit by Laxative Subgroup (Least Squares Mean ± Standard Error)**
Subjects on a Stable Laxative Regimen – Intent-to-Treat Population

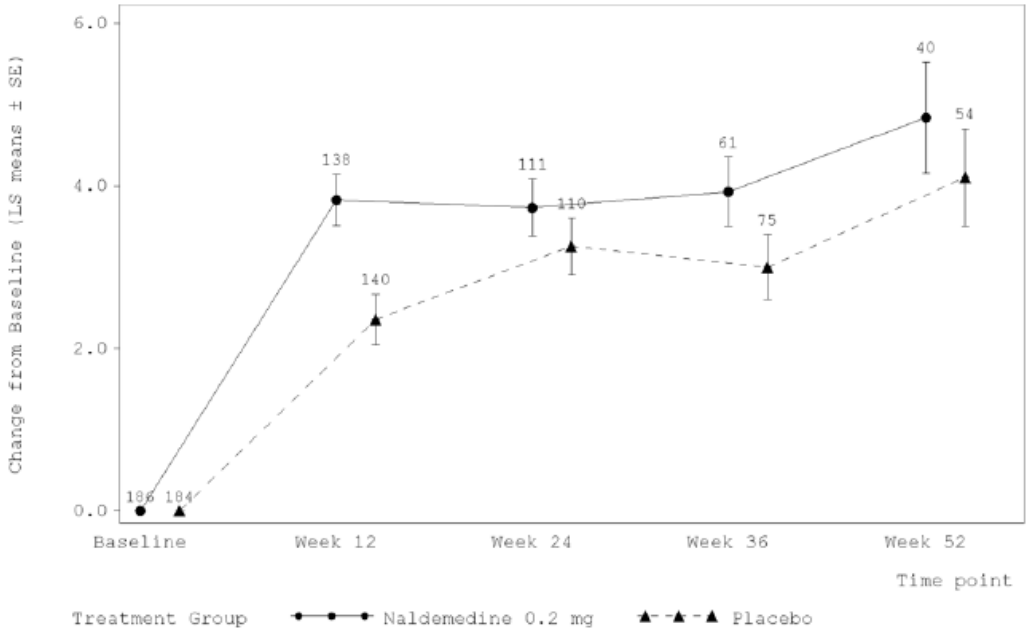


Baseline was 14 consecutive calendar day qualifying period during the Screening Period.

Frequency of BMs per week was calculated as the weekly average of observations in 7 days prior to each visit.

Number of subjects at each visit is shown in the figure.

Figure 11-3 **Change in the Frequency of Bowel Movements per Week from Baseline to Each Visit by Laxative Subgroup (Least Squares Mean ± Standard Error)**
Subjects not on a Stable Laxative Regimen – Intent-to-Treat Population



Baseline was 14 consecutive calendar day qualifying period during the Screening Period.
Frequency of BMs per week was calculated as the weekly average of observations in 7 days prior to each visit.
Number of subjects at each visit is shown in the figure.

Change in PAC-SYM scores:

For subjects on a stable laxative regimen:

- Subjects in the naldemedine group had a greater improvement from baseline in the mean overall PAC-SYM score over time than subjects in the placebo group with treatment effects varying from -0.15 to -0.36. The difference was significant at all time points apart from the last.
- For the stool-symptoms domain a statistically significant greater improvement in the naldemedine group was seen at all time points.
- For the abdominal-symptoms and rectal-symptoms domains a numerically greater improvement was seen in the naldemedine group at all time points, however only statistically significant at some time points.

For subjects not on a stable laxative regimen:

- Subjects in the naldemedine group had a greater improvement from baseline in the mean overall PAC-SYM score over time than subjects in the placebo group with treatment effects varying from -0.24 to -0.45. The difference was significant at all time points.
- For the stool-symptoms domain a statistically significant greater improvement in the naldemedine group was seen at all time points.

- For the abdominal-symptoms and rectal-symptoms domains a numerically greater improvement was seen in the naldemedine group at all time points, however only statistically significant at some time points.

Change in PAC-QOL scores:

For subjects on a stable laxative regimen:

- Subjects in the naldemedine group had a greater improvement from baseline in the mean overall PAC-SYM score over time than subjects in the placebo group with treatment effects varying from -0.20 to -0.39. The difference was significant at all time points.
- For all the domain scores a significantly greater improvement from baseline in the naldemedine group compared to placebo was seen at most time points.

For subjects not on a stable laxative regimen:

- Subjects in the naldemedine group had a greater improvement from baseline in the mean overall PAC-SYM score over time than subjects in the placebo group with treatment effects varying from -0.35 to -0.50. The difference was significant at all time points.
- For all the domain scores a significantly greater improvement from baseline in the naldemedine group compared to placebo was seen at most time points.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18 Summary of Efficacy for Trial V9235

Title: A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Phase 3 Study to Evaluate the Long-term Safety of Naldemedine for the Treatment of Opioid-induced Constipation in Subjects with Non-malignant Chronic Pain Receiving Opioid Therapy		
Study Identifier	1326V9235	
Design	Phase 3, randomised, double-blind, placebo-controlled, parallel-group long-term study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks treatment and 14 days follow-up 2-4 weeks screening phase not applicable
Hypothesis	Superiority	
Treatment Groups	Naldemedine 0.2 mg	Naldemedine oral tablet 0.2 mg QD for 52 weeks, 623 patients randomised
	Placebo	Placebo QD for 52 weeks, 623 patients randomized

Endpoints and Definitions	Secondary endpoint	Change in frequency of BM/week	Change from baseline in frequency of BMs at weeks 12, 24, 36 and 52.
	Secondary endpoint	Subjects with use of rescue laxatives	Rescue was defined as any laxative taken for the first time during the treatment period. Use of rescue was summarized for subjects not on stable laxatives (subjects who did not have laxative use reported or received only rescue) and subjects on stable laxatives (subjects who might have at least one/any stable laxative use reported).
	Secondary endpoint	Change in PAC-SYM	Change from baseline in PAC-SYM overall score at weeks 2, 12, 24, 36 and 52.
	Secondary endpoint	Change in PAC-QOL	Change from baseline in PAC-QOL overall score at weeks 2, 12, 24, 36 and 52.
Database Lock	29 February 2016		
Results and Analysis			
Analysis Description	**Secondary Analysis**		
Analysis Population and Time Point Description	Intent-to-treat (all subjects randomised), results for various timepoints during the 52-week treatment period as detailed below		
Descriptive Statistics and Estimate Variability	Treatment group	Naldemedine 0.2 mg	Placebo
	Number of subjects	621	620
	Change in frequency of BM/week at Week 12 (LS mean)	3.70	2.42
	SE	0.163	0.162
	Change in frequency of BM/week at Week 24 (LS mean)	3.77	2.77
	SE	0.172	0.172
	Change in frequency of BM/week at Week 36 (LS mean)	3.88	2.88
		0.180	0.177
	Change in frequency of BM/week at Week 52 (LS mean)	3.92	2.92

	SE	0.184	0.187
	Rescue laxative use: Not on stable laxatives On stable laxatives	 12/186 (6.5%) 23/314 (7.3%)	 22/184 (12.0%) 41/336 (12.2%)
	Change in PAC-SYM at Week 12 (LS mean)	-1.11	-0.86
	SE	0.039	0.039
	Change in PAC-SYM at Week 52 (LS mean)	-1.22	-0.98
	SE	0.041	0.042
	Change in PAC-QOL at Week 12 (LS mean)	-1.19	-0.83
	SE	0.036	0.037
	Change in PAC-QOL at Week 52 (LS mean)	-1.24	-0.94
	SE	0.039	0.040

Effect Estimate Per Comparison	Change in frequency of BM/week at Week 12	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	1.28
		95% CI for difference	0.83, 1.72
		P-value (MMRM)	<0.0001
	Change in frequency of BM/week at Week 24	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	1.00
		95% CI for difference	0.53, 1.47
		P-value (MMRM)	<0.0001
	Change in frequency of BM/week at Week 36	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	1.01
		95% CI for difference	0.52, 1.50
		P-value (MMRM)	<0.0001
	Change in frequency of BM/week at Week 52	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	1.00
		95% CI for difference	0.49, 1.51

		P-value (MMRM)	0.0001
	Change in PAC-SYM at Week 12	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	-0.25
		95% CI for difference	-0.36, -0.14
		P-value (MMRM)	<0.0001
	Change in PAC-SYM at Week 52	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	-0.24
		95% CI for difference	-0.35, 0.12
		P-value (MMRM)	<0.0001
	Change in PAC-QOL at Week 12	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	-0.36
		95% CI for difference	-0.46, -0.26
		P-value (MMRM)	<0.0001
	Change in PAC-QOL at Week 52	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	-0.31
		95% CI for difference	-0.42, -0.20
		P-value (MMRM)	<0.0001
Notes	The MMRM model has the terms for treatment group, time, treatment-by-time as a fixed effect. Results for PAC-SYM and PAC-QOL were consistent across all visits assessed but are shown here for Week 12 and Week 52 only		
Abbreviations/Definitions	BM=bowel movement; MMRM=Mixed-Effect Model Repeated Measures; CI=confidence interval; PAC-SYM= Patient Assessment of Constipation Symptoms Questionnaire; PAC-QOL= Patient Assessment of Constipation Quality of Life Questionnaire; LS mean=least squares mean; QD=once daily; SE=standard error		

Trial V9236

Trial V9236 is entitled "A phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group study of naldemedine in cancer patients with opioid-induced constipation".

The trial was a randomized, double-blind, placebo-controlled, parallel-group, multicentre trial comparing efficacy and safety of 0.2 mg QD naldemedine versus placebo. The trial consisted of a 14-28-day screening period, a 14 days treatment period, and a 4-week follow-up period.

At visit 1 subjects were screened to determine eligibility. Subjects provided the investigator with details of their regular-use laxative regimen. This regimen was maintained throughout the screening period. At visit 2, up to 28 days later, subjects were randomised to treatment with either naldemedine or placebo for 2 weeks.

During the treatment period subjects attended 3 scheduled visits: baseline/randomisation (Visit 2), Day 8 (Visit 3), and Day 15 (Visit 4), and completed the diary evaluating bowel movement daily. The PAC-SYM/PAC-QOL was completed at Day 1 and Day 15.

Methods

Study Participants

The trial was conducted in cancer patients with OIC and investigated the effect of naldemedine relative to placebo. Subjects on a stable laxative regimen at screening would to continue on that regimen.

The main inclusion criteria were

- Diagnosis of cancer and OIC
- Cancer condition expected to be stable during the study period
- Age 20 years or older
- Treatment with opioids (regular-use) for at least 2 weeks prior to screening, and treatment with a stable opioid regimen for 14 days prior to randomisation (100 to 150% of the dose of regular-use opioids on the day of 14 days prior to the randomisation)
- At most 5 SBMS during 14 consecutive days prior to randomisation with one or more of the following bowel symptoms in 25% or more of all BMs regardless of use of rescue laxatives.
    - Straining during bowel movement (2 (moderate) or above on straining symptom score)
    - Feeling of incomplete evacuation
    - Passage of hard stools or pellets (1 or 2 on Bristol stool form scale)

Note that a BM occurring within 24 hours after rescue laxatives does not count as an SBM.

- Subjects who could walk and carry out daily activities without assistance (0 to 2 on performance status of Eastern cooperative oncology group)
- Subjects who could assess the condition (reccordance in the diary by somebody on behalf of the subject was allowed)

The main exclusion criteria were

- Subjects who had never taken laxatives for the treatment of OIC
- Subjects who had reported no bowel movements for 7 consecutive days prior to the treatment period
- Subjects treated with chemotherapy with known gastro intestinal effects

Trial drug was to be discontinued for any of the following reasons:

- Worsening of the target disease, for instance progression of cancer, worsening of constipation
- On the discretion of the investigator because of safety concerns or other reasons
- Subjects was proved to be ineligible for the study
- If the subject met the liver discontinuation criteria (abnormal liver function test)
- Lost to follow-up

Withdrawal from the trial: subjects may voluntarily withdraw from the trial for any reason at any time. For withdrawn subjects every effort is made to complete the end-of-study (or early termination) assessments. All subjects who withdrew or discontinued due to an AE were to be followed until resolution of such AE or until the unresolved adverse events were judged by the investigator to have stabilised, or lost to follow-up.

Treatments

Patients were randomized 1:1 to receive either naldemedine 0.2 mg QD or placebo tables matching 0.2 mg naldemedine QD orally. Every effort was to be made to take the study drug at approximately the same time each day regardless of meal conditions. However on day 2, patients must have received the study drug 24 hours or more after the first administration of the study drug.

Opioid treatment: The stable opioid regimen from the before randomisation should be kept throughout the trial.

Laxatives: If subjects were on a laxative regimen prior to the study that regimen should be maintained throughout the study. Temporarily discontinuation or dose-reduction was allowed in case the investigator was concerned about the effect of AE on the subject's quality of life.

Rescue medication: Rexcue laxatives were allowed as-needed, but prohibited 24 hours before and after the first dose of the study drug. A BM occurring within 24 hours after rescue therapy was not counted as an SBM.

Objectives

Primary objective: To compare the efficacy assessed over 14 day's treatment based on the responder proportion of naldemedine 0.2 mg QD versus placebo in subjects with cancer and OIC.

Secondary objectives:

- To evaluate the efficacy of naldemedine compared to placebo for the secondary endpoint
- To evaluate the safety of naldemedine compared to placebo
- To assess the pharmacokinetic profiles of naldemedine and its metabolite nor-naldemedine.

Outcomes/endpoints

A response week was defined as at least 3 SBMS per week and an increase from baseline of at least 1 SBM per week for that week. Baseline was defined as the average number of SBMs per week during the 14-day period prior to the treatment period. (Response for CSBM was defined similarly). The primary efficacy endpoint was the proportion of SBM responders during the 2-week treatment period.

Secondary endpoints were:

- Proportion of patients with CSBM response during the 2-week treatment period

- Proportion of patients with SBM/CSBM response for each week during the 2-week treatment period
- Changes in frequency of SBMs/CSBMs per week from baseline during the 2-week treatment period
- Weekly change in the frequency of SBMs/CSBMs per week from baseline during the 2-week treatment period
- Time to first SBM/CSBM after the first administration of study drug
- Daily change in the frequency of SBMs from baseline during the 2-week treatment period
- Change in the number of days with at least 1 SBM/CSBM per week from baseline during the 2-week treatment period
- Proportion of patients with at least 1 SBM/CSBM for each observation time point within 24 hours after the first administration of study drug during the 2-week treatment period
- Change in the frequency of SBMs with BSS score of 3 or 4 per week from baseline during the 2-week treatment period
- Change in the frequency of SBMs per week without straining from baseline during the 2-week treatment period
- Change in the frequency of use of rescue laxatives per week from baseline during the 2-week treatment period
- Weekly change in the abdominal bloating and abdominal discomfort scores from baseline during the 2-week treatment period
- Change in PAC-SYM and PAC-QOL from baseline to each observation time point
- Proportion of patients with PAC-SYM respectively PAC-QOL response

Sample size

Based on previous study experience a conservative assumption of 37.5% responders in the placebo group and a 23.5% difference between the two groups was assumed. In order to have at least 90% power for detecting such a difference between the two groups for a 2-sided 5% significance level using the chi-squared test a total of 188 subjects need to be randomised. Moreover based on previous experience it is assumed that 1% of subjects randomised will be excluded from FAS, thus 190 subjects were planned to be enrolled.

Randomisation

At visit 2, eligible patients were randomised in a 1:1 manner to one of the treatment groups. The interactive web-response system IWRS was used to assign patients to numbers for which treatment had already been randomly assigned. The randomisation was completed with the stochastic minimisation method to adjust patient numbers so that the difference in the numbers did not exceed 2 between the treatment groups in participating study sites.

Blinding (masking)

The trial was conducted in a double-blind manner by using matching placebo canisters in appearance, labelling, and packaging. Moreover the test drug and placebo were indistinguishable in terms of appearance, shape, and smell.

All subjects, study personnel, and data analysts were blinded to the treatment assigned at randomisation until database lock. The randomisation schedule was only accessible to the person responsible for the study drug assignment and the person responsible for the bioanalytical laboratory. Plasma drug concentration were only reported to the sponsor after the database was locked. During the trial the investigator could perform an emergency unblinding for AEs if the safety of the patients was at risk. In such case the sponsor was notified and the date and reason for the unblinding was recorded in the source documents.

Statistical methods

Primary endpoint:

A response week was defined as at least 3 SBMS per week and an increase from baseline of at least 1 SBM per week for that week. Baseline was defined as the average number of SBMs per week during the 14-day period prior to the treatment period. (Response for CSBM was defined similarly).

The frequency of SBMs per week was defined as 7*(total frequency of SBMs during the treatment period)/(Number of days in the treatment period).

The change in frequency of SBMs per week was defined as (Frequency of SBMs per week in the 2-week treatment period)-(Frequency of SBMs per week in the baseline period).

The definitions for CSBM were similar.

The primary efficacy endpoint was the proportion of SBM responders during the 2-week treatment period.

Analysis populations:

FAS: All randomised subjects who received at least 1 dose of study drug and had an evaluation of OIC at baseline and at least another evaluation of OIC after the initiation of study drug.

PPS: All randomised subjects meeting the following criteria:

- Met all inclusion criteria and no exclusion criteria
- No major deviations of study procedure
- Appropriate follow-up

Major protocol deviations were identified before unblinding the database. For both analysis populations subjects were analysed as randomised.

Handling of missing values:

Missing values of frequency of SBMs per week were imputed using last observation carried forward.

If more than 50% of the PAC-QOL items of a domain were missing, the mean score for that domain was set to missing. If PAC-QOL was missing for at least 1 domain, the overall score was set to missing.

Statistical analysis of primary endpoint:

The proportion of SBM responders during the 2-week treatment period were compared between the two treatment groups using chi-square test for the FAS. Moreover confidence intervals for proportions and the difference between proportions will be calculated using the Clopper-Pearson method. The comparison was also done for PPS as a sensitivity analysis.

Statistical analysis of secondary endpoints:

All secondary endpoints were analysed on FAS.

A PAC-SYM responder was defined as a patient with at least a 1 point improvement in PAC-SYM from baseline. A PAC-QOL responder was defined as a patient with at least a 1 point improvement in the PAC-QOL domain "dissatisfaction" from baseline.

Proportions of patients with CSBM response during the 2-week treatment period, the proportion of SBM/CSBM responders during each observation week, the proportion of patients with at least 1 SCBM//CSBM for each observation time point within 24 hours after the first administration of study drug during the 2-week treatment period, and proportion of PAC-SYM/PAC-QOL responders was analysed similarly to the primary endpoint.

Change in frequency from baseline to different time periods were compared between naldemedine and placebo groups using analysis of covariance (ANCOVA) with frequency at baseline as a covariate. This type of analysis was done for:

- Change in the frequency of SBMs/CSBMs per week from baseline during the 2-week treatment period
- Change in the frequency of SBMs with BSS score of 3 or 4 per week from baseline during the 2-week treatment period
- Change in the frequency of SBMs per week without straining from baseline during the 2-week treatment period
- Change in the number of days with at least 1 SBM/CSBM per week from baseline during the 2-week treatment period

Weekly change in frequency per week from baseline during the 2-week treatment will be done using MMRM including treatment group, week, and week-by-treatment group interaction as fixed factors, and the frequency at baseline as covariate. An unstructured covariance matrix within subjects will be assumed.

This type of analysis was done for:

- Weekly change in the frequency of SBMs/CSBMs per week from baseline during the 2-week treatment period
- Weekly change in the frequency of SBMs per week without straining from baseline during the 2-week treatment period
- Weekly change in the frequency of SBMs with BSS score of 3 or 4 per week without straining from baseline during the 2-week treatment period
- Daily change in the frequency of SBMs from baseline during the 2-week treatment period (substituting week with day in the model description above)

- Weekly change in the abdominal bloating and abdominal discomfort scores from baseline during the 2-week treatment period

Time to first SBM/CSBM after the first administration of study drug is presented in a Kaplan-Meier plot, and median time with CI is calculated for each treatment group. The distribution of times was compared between groups using a generalized Wilcoxon test.

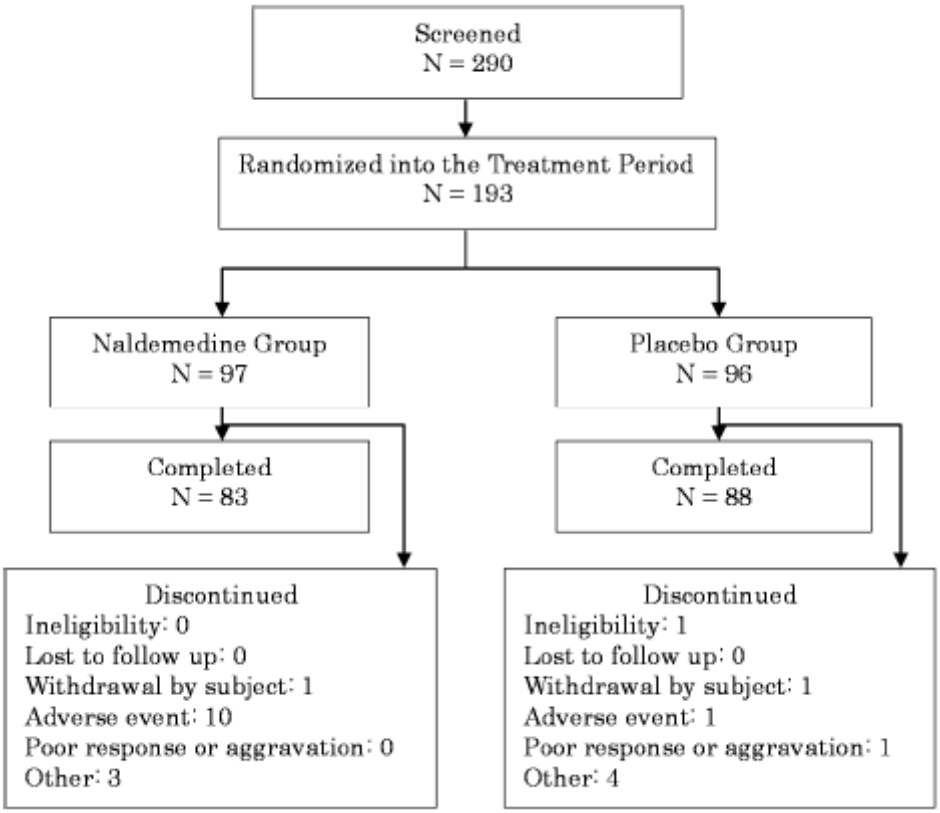
Change in frequency of rescue-use laxative per week from baseline during the 2-week treatment period was compared between naldemedine and placebo using the Wilcoxon rank-sum test.

Mean changes in the scores for PAC-SYM/PAC-QOL and their domains were compared between naldemedine and placebo using a t-test.

Results

Participant flow

A total of 290 subjects were screened. Out of these 97 (33%) failed screening resulting in a total of 193 subjects randomised, 97 to naldemedine and 96 to placebo with respectively 83 (85.6%) and 88 (91.7%) completing the study. The main reasons for discontinuation were adverse events and other. Adverse events were much more common for subjects on naldemedine (10.3% compared to 1.0%).
In the naldemedine group 5 subjects withdrew due to diarrhoea, the other AEs belonging to the SOC of infections and infestations or a different SOC. Apart from this, reasons for withdrawal seemed balanced and completion rates comparable and reasonably high.



Recruitment

The trial was a multicentre trial with 70 sites in Japan. The first subject was enrolled in November 2013 and the last subject completed in April 2015.

Conduct of the study

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice. The original protocol dated 24 September 2013 was amended on 23 October 2013 before the first subject was enrolled.

Baseline data

The demographic characteristics of the FAS population were generally well balanced across treatment groups. The mean age was around 64 years with about 90% of subjects being 50 years or above. The majority of patients were male (61.7%) and all were Asian from Japan. The study population had a mean weight of 55 kg, and only a minority of subjects (approximately 12%) were overweight or obese (BMI above 25 kg/m2). The majority of subjects had performance status 1 (54%), and 32% respectively 15% had performance status 0 and 2.

At baseline, the mean regular-use opioid per day (dose of opioid analgesics converted into equivalent oral morphine dose) was 57.3 mg for the naldemedine group and 69.5 mg for the placebo group. The maximum dose was 270 mg for naldemedine and 720 mg for placebo.

		Naldemedine 0.2 mg N=97 n (%)	Placebo N=96 n (%)	P-value [a]
Baseline Regular-Use Opioid per Day (mg) [b]	n	97	96	Pt=0.2789
	Mean	57.3	69.5	
	SD	46.4	99.5	
	Min	6	15	
	Median	46.5	35.0	
	Max	270	720	
	<15	2 (2.1)	1 (1.0)	
	>=15 to <30	24 (24.7)	27 (28.1)	
	>=30 to <60	24 (24.7)	29 (30.2)	
	>=60 to <120	34 (35.1)	25 (26.0)	
	>=120	13 (13.4)	14 (14.6)	

The mean SBMs per week was around 1 with a median of also 1.

All subjects had cancer and were treated with opioids. The primary tumour was lung (43.5%), breast (19.5%), large intestine (3.1%), and other (31.6%). In total 87.6% had metastasis. About a third of subjects had a previous medical condition, and almost all subject had concurrent medical condition.

Regular-use opioid therapy was received by all subjects during both the screening period and the treatment period, most frequently oxycodone and fentanyl. Rescue-use opioid therapy was received by a similar proportion in the two groups (63.9% for naldemedine and 61.5% for placebo during screening, and 66.0% for naldemedine and 61.5% for placebo during treatment).

The most commonly reported concurrent medical conditions were hypertension (33.7%), insomnia (34.7%), diabetes mellitus (11.9%), and decreased appetite (11.4%).

Numbers analysed

A total of 193 subjects were randomised, 97 to naldemedine and 96 to placebo. They were all included in the FAS. In both treatment groups 17 subjects were excluded from the PPS. One subjects in the naldemedine group, and 2 subjects in the placebo group, were excluded because of ineligibility. The rest were excluded because of treatment violation, which was defined as deviation of the concomitant medicine, treatment compliance less than 80%, or that the treatment period ended prior to day 15 to 17.

Table 10-2 Analysis Populations: All Randomized Patients

	Naldemedine 0.2 mg N=97 n (%)	Placebo N=96 n (%)	P-value [a]
Patients included in FAS	97 (100.0)	96 (100.0)	---
Patients excluded from FAS	---	---	
Reason for exclusion			
- No efficacy data after randomization	---	---	
- Patients who received no study drug	---	---	
Patients included in PPS	80 (82.5)	79 (82.3)	1.0000
Patients excluded from PPS	17 (17.5)	17 (17.7)	
Reason for exclusion			
- No efficacy data after randomization	---	---	
- Ineligible patients	1 (1.0)	2 (2.1)	
- Patients who received no study drug	---	---	
- Patients with treatment violation [b]	16 (16.5)	15 (15.6)	
- Patients with inappropriate follow-up	---	---	

[a] Fisher's exact test.

[b] Patients with deviation of the concomitant medicine, treatment compliance < 80%, or Treatment Period ended prior to Visit 4 (Day 15 to 17).

Table 10-1 Important Protocol Deviations: All Randomized Patients

	Naldemedine 0.2 mg N=97	Placebo N=96	FAS	PPS	Safety
Violation of the inclusion criteria					
– The patient did not satisfy the inclusion criterion #8. (The description about the bowel movement of the patient's diary was not clear during the Screening Period.)	0	1	Y	N	Y
– The patient did not satisfy the inclusion criterion #5. (The patient was experiencing the bowel symptoms in less than 25% of bowel movements.)	0	1	Y	N	Y
Violation of the exclusion criteria					
– The patient met the exclusion criterion #1. (The patient started receiving the new anti-malignant tumor drug in the 2 weeks prior to Screening.)	2	0	Y	N [a]	Y
Violation of the study methods					
– The rescue-use laxative was administrated within 24 hours after initial dosing of the study drug.	1	4	Y	N	Y
– The study drug was administrated twice a day.	0	1	Y	N	Y
– The rate of days with non-compliance of the study drug exceeded 20%.	9	4	Y	N	Y
– Violation of the concomitant drugs	1	1	Y	N	Y

Y shows including in the analysis data set; N shows excluding from the analysis population.

[a] Of the 2 patients, 1 patient (Patient ID 9GB004) received new cancer chemotherapy (bevacizumab) from 2 weeks prior to Screening . The Sponsor proposed that the patient should be excluded from PPS Population in accordance with the standards for handling cases. However, medical experts considered that there was no effect on efficacy of the study drug with consideration for profile of bevacizumab. Therefore the Sponsor decided that the patient was included in the PPS Population.

Outcomes and estimation

Primary analysis:

The proportion of SBM responders during the 2-week treatment period was 71.1% for naldemedine and 34.4% for placebo. The treatment effect was 36.76% and was statistically significant. The sensitivity analysis using PPS instead of FAS gave a very similar result, with a treatment effect of 37.06%. An additional post-hoc analysis compared the proportions using the Cochran-Mantel-Haenszel test and stratifying by opioid group (< 60 mg and ≥ 60 mg). The overall result was very similar, but it is worth noting that the placebo group response varies by opioid group dose.

Table 11-1 SBM Responder During the 2-Week Treatment Period: FAS

Time Point			Naldemedine 0.2 mg N=97	Placebo N=96
2-Week Treatment Period	Proportion [a]		71.1% (69/97)	34.4% (33/96)
	95% Confidence Interval [b]		61.05%, 79.89%	24.98%, 44.77%
	Comparison with placebo	Difference of Proportion (SE)	36.76% (6.68%)	
		95% CI for Difference	23.66%, 49.86%	
		P-value [c]	**<.0001**	

SE, Standard error; CI, Confidence interval

[a] Proportion = Proportion of SBM Responders

[b] The 95% confidence interval is calculated by using Clopper-Pearson method.

[c] P-value is from the chi-square test.

Table 11-3 SBM Responder During the 2-week Treatment Period: Adjusted by the Stratified Opioid Groups: FAS

Time Point			Naldemedine 0.2 mg N=97	Placebo N=96
2-Week Treatment Period	Proportion [a]		71.1% (69/97)	34.4% (33/96)
	95% Confidence Interval [b]		61.05%, 79.89%	24.98%, 44.77%
	Stratified Opioid Dose Group (mg)	< 60	72.0% (36/50)	40.4% (23/57)
		>= 60	70.2% (33/47)	25.6% (10/39)
	Comparison with placebo	Difference of Proportion (SE) [c]	37.39% (6.70%)	
		95% CI for Difference	24.27%, 50.52%	
		P-value [d]	**<.0001**	

SE, Standard error; CI, Confidence interval

[a] Proportion = Proportion of SBM Responders

[b] The 95% confidence interval is calculated by using Clopper-Pearson method.

[c] Difference of Proportion (SE) is calculated by using the estimator given by Koch et al.

[d] P-value is from the Cochran-Mantel-Haenszel test adjusted by the stratified opioid dose group.

Secondary efficacy analyses:

- The proportion of CSBM responders during the 2-week treatment period was 40.2% for naldemedine and 12.5% for placebo. The treatment effect was 27.71% and was statistically significant.

Table 11-4 CSBM Responder During the 2-Week Treatment Period: FAS

Time Point			Naldemedine 0.2 mg N=97	Placebo N=96
2-Week Treatment Period	Proportion [a]		40.2% (39/97)	12.5% (12/96)
	95% Confidence Interval [b]		30.37%, 50.65%	6.63%, 20.82%
	Comparison with placebo	Difference of Proportion (SE)	27.71% (6.01%)	
		95% CI for Difference	15.92%, 39.49%	
		P-value [c]	**<.0001**	

SE, Standard error; CI, Confidence interval

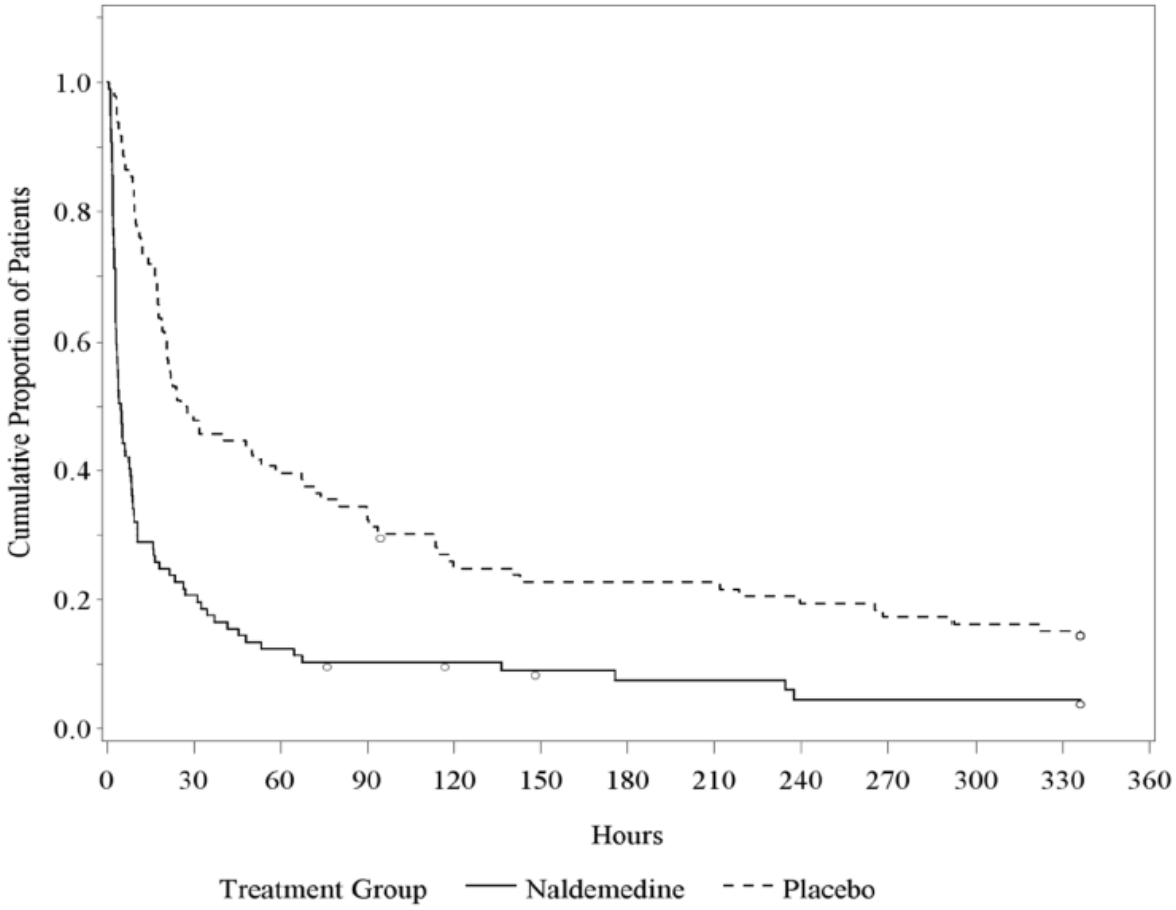
[a] Proportion = Proportion of CSBM Responders

[b] The 95% confidence interval is calculated by using Clopper-Pearson method.

[c] P-value is from the chi-square test.

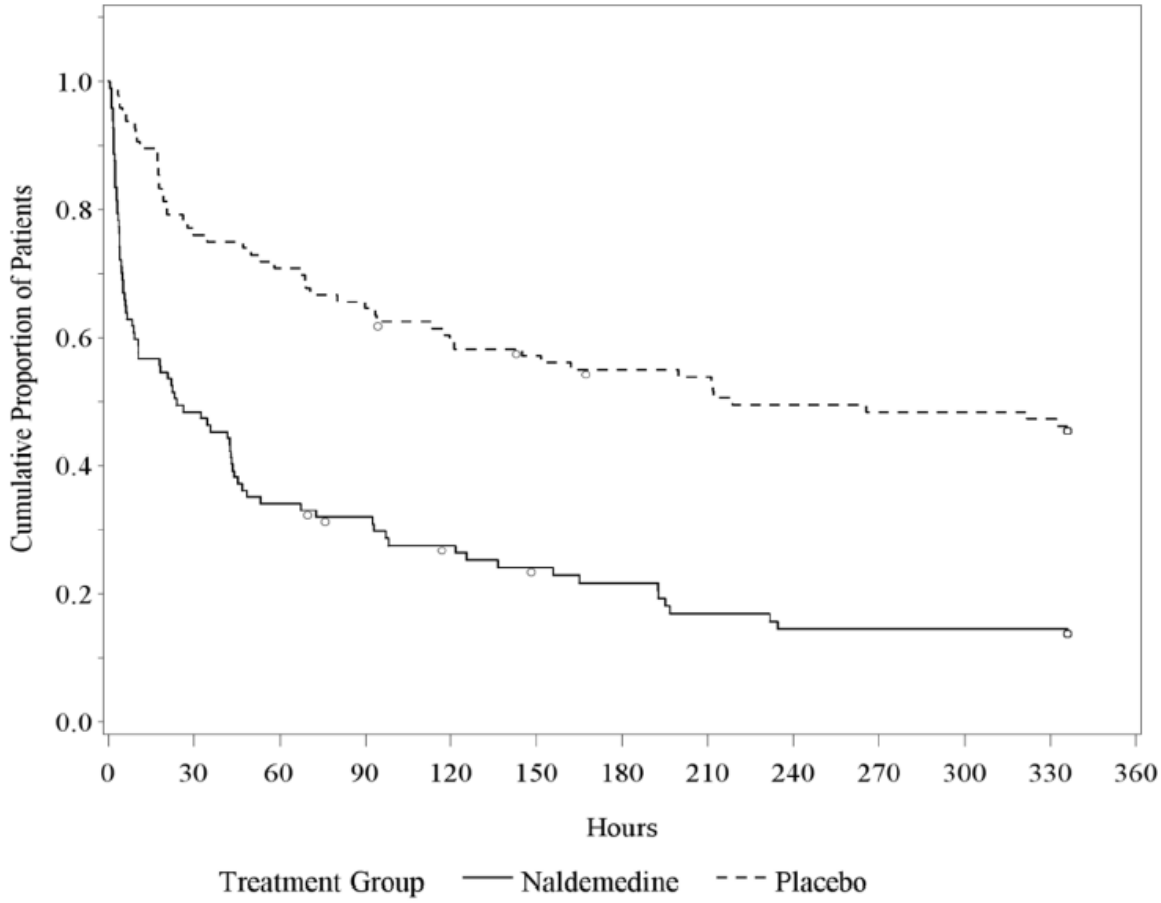
- The proportion of SBM responders were 77.3% and 44.8% at Week 1 and 66.0% and 31.3% at Week 2 for naldemedine respectively placebo. The treatment effects were 32.53% at Week 1 and 34.73% at Week 2, both statistically significant. Similarly the CSBM responders were 49.5% and 15.6% at Week 1 and 44.3% and 14.6% at Week 2 for naldemedine respectively placebo. The treatment effects were 33.86% at Week 1 and 29.75% at Week 2, both statistically significant.
- The treatment difference for naldemedine relative to placebo in changes from baseline of SBMs/CSBMs per week during the 2-week treatment period was 3.62 SBMs/2.05 CSBMs, both statistically significant.
- For the weekly change in frequency from baseline the difference between naldemedine and placebo was 3.97 SBMs/2.52 CSBMs at Week 1, and 2.73 SBMs/1.37 CSBMs at Week 2, all statistically significant.
- The median time to first SBM/CSBM after first study drug administration was 4.67/24.00 hours for naldemedine and 26.58/218.50 hours for placebo, the differences being statistically significant.

Figure 11-1 Kaplan-Meier Curve of Time to First SBM: FAS



The circle in the figure represents censored time.

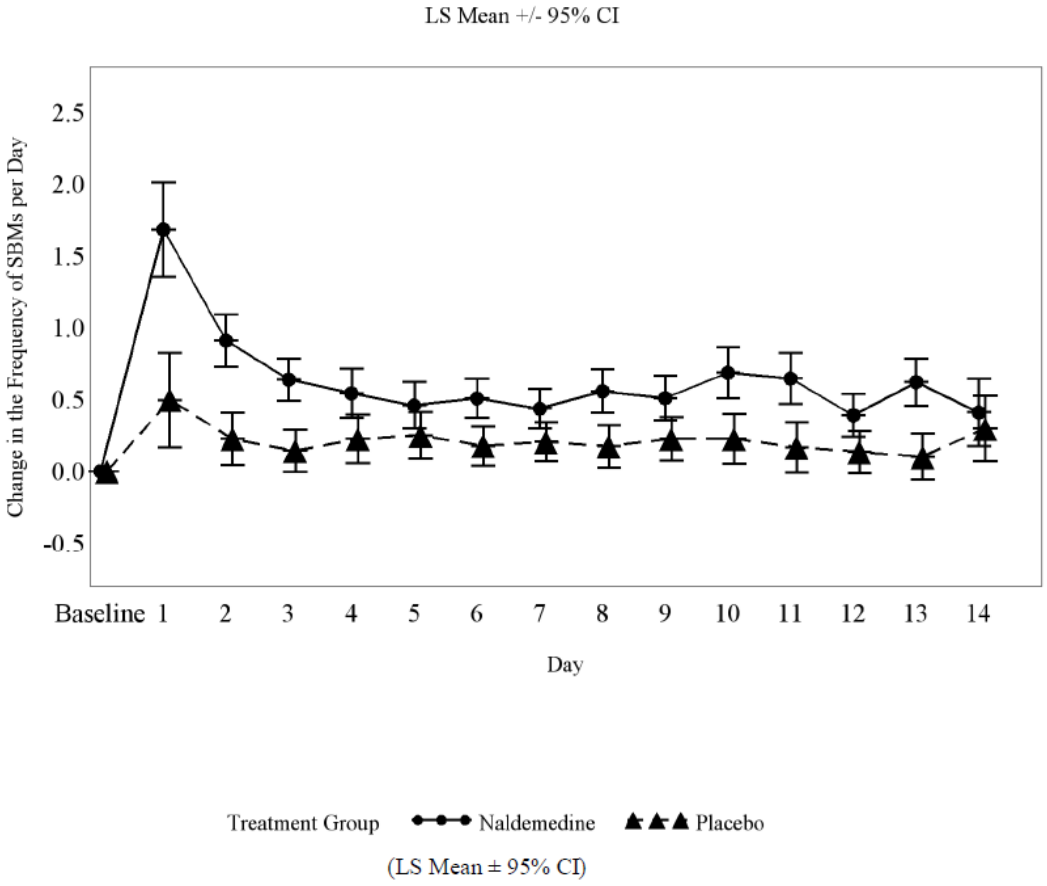
Figure 11-2 Kaplan-Meier Curve of Time to First CSBM: FAS



The circle in the figure represents censored time.

- The difference between the groups in change from baseline in the frequency of SBMS per day was statistically significant on most observation days. Note that the largest treatment effect is seen on Day 1, thereafter it is more or less stable.

Figure 11-3 Time Course of Change in the Frequency of SBMs per Day: FAS



- The difference between naldemedine and placebo in change from baseline in number of days with at least 1 SBM/CSBM per week was 1.62 days (SBM) /1.23 days (CSBM), both statistically significant. For weekly change from baseline in number of days with at least 1 SBM/CSBM per week the difference between naldemedine and placebo was 1.72 SBMs/1.47 CSBMs at Week 1, and 1.54 SBMs/0.98 CSBMs at Week 2, all statistically significant.
- The proportion of subjects with at least 1 SBM/CSBM for each of the observation time points 4, 8, 12, and 24 hours after the initial administration of study drug was higher for naldemedine than placebo. For SBM the treatment effects (difference of proportions) were 41.16%, 46.24%, 46.13%, and 29.40%, whereas for CSBM the treatment effects were 23.67%, 30.86%, 43.3%, and 50.5%. All were statistically significant.
- The treatment difference for naldemedine relative to placebo in changes from baseline of frequency of SBMs with Bristol stool scale of 3 or 4 per week during the 2-week treatment period was 0.64 SBMs, statistically significant.
- For the weekly change from baseline in frequency of SBMs with Bristol stool scale of 3 or 4 the difference between naldemedine and placebo was 0.72 at Week 1, and 0.60 at Week 2, both statistically significant.

- The treatment difference for naldemedine relative to placebo in changes from baseline of frequency of SBMs without straining per week during the 2-week treatment period was 2.67 and statistically significant.
- For the weekly change from baseline in frequency of SBMs without straining, the difference between naldemedine and placebo was 3.13 at Week 1, and 1.52 at Week 2, both statistically significant.
- The change from baseline in frequency of laxative use per week during the 2-week treatment period was -2.98 for naldemedine and -1.13 for placebo. The difference was statistically significant.
- The treatment difference for naldemedine relative to placebo in changes from baseline in abdominal bloating scores during the 2-week treatment period was 2.67 and statistically significant.
- For the weekly change from baseline in abdominal bloating scores the difference between naldemedine and placebo was -0.15 at Week 1, and -0.14 at Week 2, statistically significant only at Week 1.
- For the weekly change from baseline in abdominal discomfort scores the difference between naldemedine and placebo was -0.16 at Week 1, and -0.11 at Week 2, statistically significant only at Week 1.
- For the PAC-SYM overall scores as well as for all domain scores, apart from the stool symptom score, there was no difference in change from baseline between naldemedine and placebo. The change from baseline in PAC-SYM stool symptoms score was more improved for naldemedine than for placebo both at Visit 4 and at last observation.
- For the PAC-QOL overall scores as well as for all domain scores, apart from the dissatisfaction score, there was no difference in change from baseline between naldemedine and placebo. The change from baseline in PAC-QOL dissatisfaction score was more improved for naldemedine than for placebo but only at Visit 4.
- The proportion of overall PAC-SYM responders were 9.8% vs. 2.3% at Visit 4 and 10.8% vs. 3.2% at the last observation for naldemedine respectively placebo. The differences were 7.48% at Visit 4 and 7.59% at last observation, both statistically significant.
- The proportion of responders for the PAC-QOL dissatisfaction domain were 34.1% vs. 18.2% at Visit 4 and 31.2% vs. 18.9% at the last observation for naldemedine respectively placebo. The differences were 15.96% at Visit 4 and 12.24% at last observation, both statistically significant.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 19 Summary of Efficacy for Trial V9236

Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of Naldemedine in Cancer Patients with Opioid-induced Constipation			
Study Identifier	1331V9236		
Design	Phase 3, randomised, double-blind, placebo-controlled, parallel-group study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		14 days treatment and 4 weeks follow-up 14-28 days screening phase not applicable
Hypothesis	Superiority		
Treatment Groups	Naldemedine 0.2 mg		Naldemedine oral tablet 0.2 mg QD for 2 weeks, 97 patients randomised
	Placebo		Placebo QD for 2 weeks, 96 patients randomized
Endpoints and Definitions	Primary endpoint	Proportion of SBM responders	A responder was defined as a subject with ≥ 3 SBMs/week and ≥ 1 SBM/week increase from baseline during the 2-week treatment period.
	Secondary endpoints	Proportion of CSBM responders	A responder was defined as a subject with ≥ 3 CSBMs/week and ≥ 1 CSBM/week increase from baseline during the 2-week treatment period.
	Secondary endpoints	Change in frequency of SBM/week	Change from baseline in frequency of SBMs from baseline during the 2-week treatment period.
	Secondary endpoint	Change in frequency of CSBM/week	Change from baseline in frequency of CSBMs from baseline during the 2-week treatment period.
Database Lock	11 May 2015		
Results and Analysis			
Analysis Description	**Primary Analysis**		
Analysis Population and Time Point Description	The Full Analysis Set Population was defined as all randomised patients who received at least 1 dose of study drug and had an evaluation of OIC at baseline and at least 1 evaluation of OIC after the initiation of study treatment. Primary efficacy results are the change from baseline over the 2-week treatment period.		

Descriptive Statistics and Estimate Variability	Treatment group	Naldemedine 0.2 mg	Placebo
	Number of subjects	97	96
	Proportion of SBM responders over 2-weeks (%)	71.1 (69/97)	34.4 (33/96)
	95% CI	61.05, 79.89	24.98, 44.77

Effect Estimate Per Comparison	SBM response rate (%)	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	36.76
		95% CI for difference	23.66, 49.86
		P-value (chi-square test)	<0.0001
Notes	The 95% CI for the proportion of responders in each treatment group was estimated by the Clopper-Pearson method. The P-value was calculated from a chi-square test		
Analysis Description	**Secondary Analysis**		

Descriptive Statistics and Estimate Variability	Treatment group	Naldemedine 0.2 mg	Placebo
	Number of subjects	97	96
	Proportion of CSBM responders over 2 weeks	40.2% (39/97)	12.5% (12/96)
	95% CI	30.37%, 50.65%	6.63%, 20.82%
	Change in SBM/week over 2 weeks (LS mean)	5.16	1.54
	SE	0.53	0.54
	Change in CSBM/week over 2 weeks (LS mean)	2.76	0.71
	SE	0.27	0.27

Effect Estimate Per Comparison	Proportion of CSBM responders over 2 weeks (%)	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	27.71
		95% CI for difference	15.92, 39.49
		P-value (chi-square test)	<0.0001
	Change in SBM/week over 2 weeks (LS mean)	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	3.62

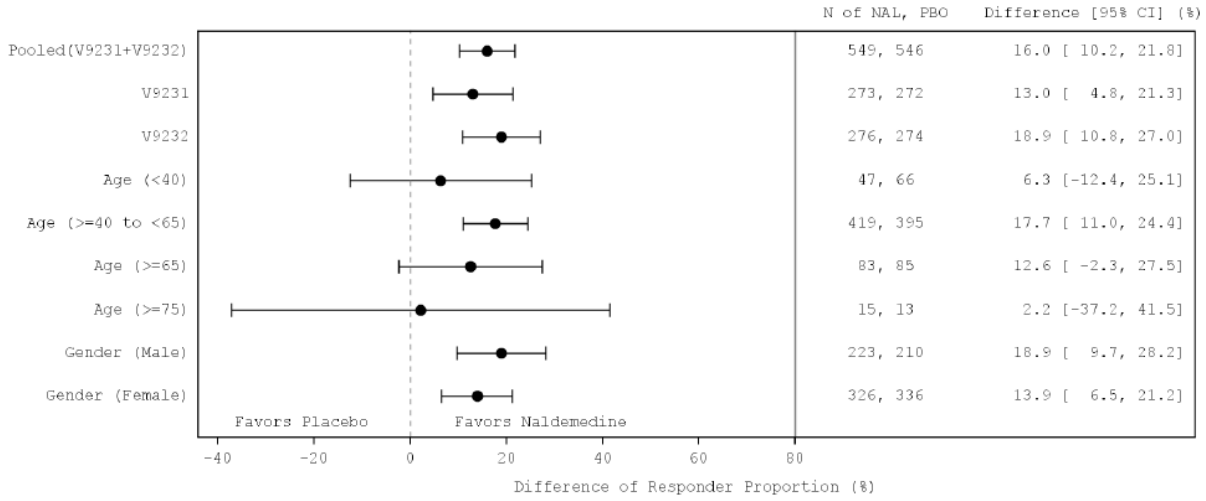
		95% CI for difference	2.13, 5.12
		P-value (ANCOVA)	<0.0001
	Change in CSBM/week over 2 weeks (LS mean)	Comparison groups	Naldemedine 0.2 mg vs placebo
		Difference in proportions	2.05
		95% CI for difference	1.29, 2.81
		P-value (ANCOVA)	<0.0001
Notes	For the proportion of CSBM responders, the P-value was calculated from a chi-square test. Statistics for change in frequency of SBM and CSBM are from an ANCOVA model with treatment group, baseline value as fixed effects.		
Abbreviations/Definitions	ANCOVA=analysis of covariance; BM=bowel movement; CI=confidence interval; CSBM=complete spontaneous bowel movement; LS mean=least squares mean; QD=once daily; SBM=spontaneous bowel movement; SE=standard error		

Analysis performed across trials (pooled analyses and meta-analysis)

- **Subgroup analyses**

Non-cancer studies:

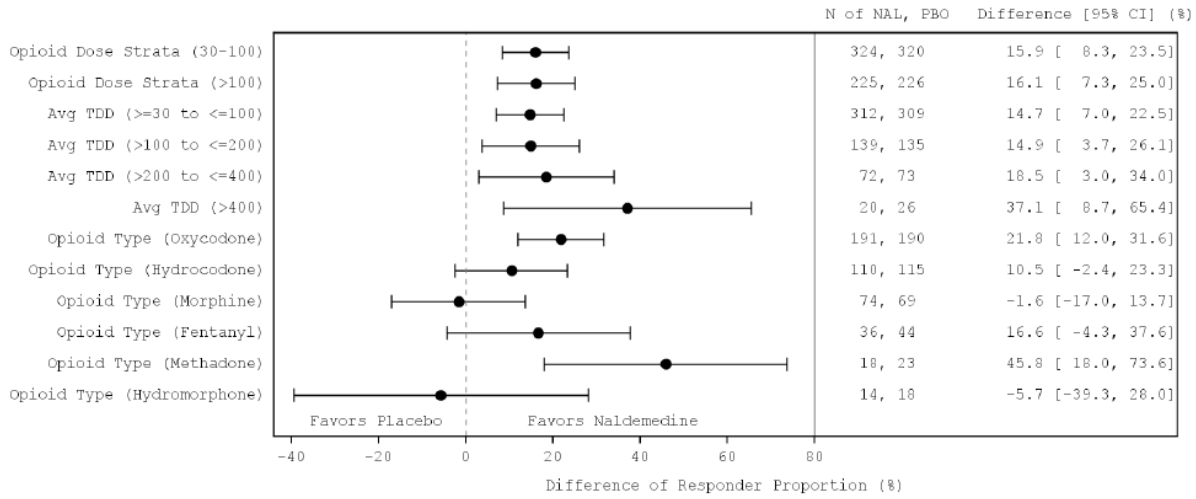
The primary endpoint was proportion of SBM responders defined as at least 3 SBMs/week with at least 1 SBM/week increase over baseline for at least 9 out of 12 weeks and at least 3 of the last 4 weeks. This was analysed according to subgroup for the individual studies V9231 and V9232, and the pool. The subgroups examined were age, gender, race, BMI, region, opioid dose strata, average TDD, opioid type, and estimated glomerular filtration rate (eGFR) at baseline. Subjects were assigned to an opioid type if the dose of that opioid corresponded to at least 75% of the total MED during the 12-week treatment period.



NAL : Naldemedine, PBO : Placebo

Source: CTD Section 5.3.5.3, Figure 14.2-1.1

Figure 7 Difference of Proportion of SBM Responders with its 95% Confidence Interval (Studies V9231 and V9232), ITT Population

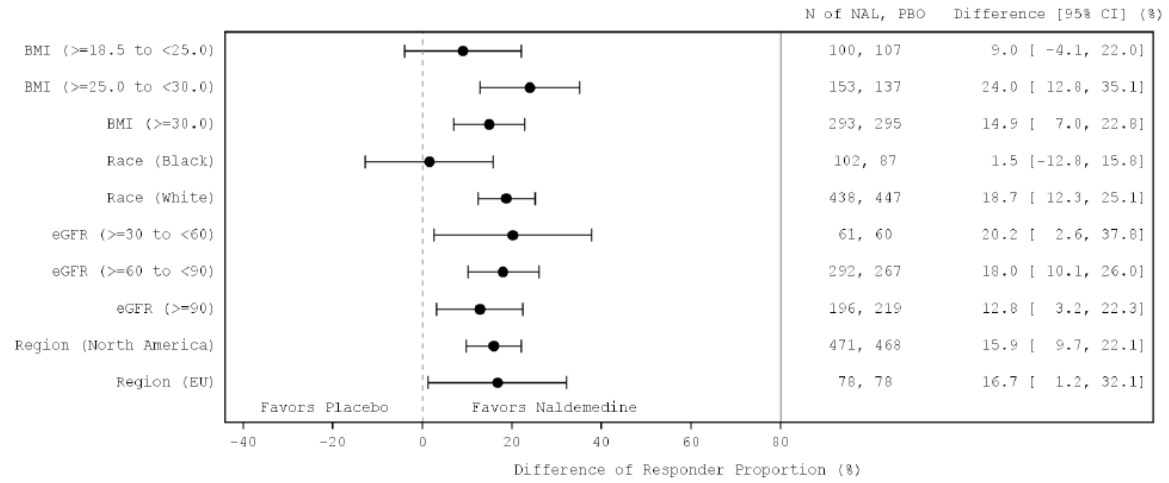


NAL : Naldemedine, PBO : Placebo

Avg TDD: Average Total Daily Dose at Baseline. Opioid type per subject was identified based on >=75% of MED.

Source: CTD Section 5.3.5.3, Figure 14.2-1.1

Figure 8 – Difference of Proportion of SBM Responders with its 95% Confidence Interval (Studies V9231 and V9232), ITT Population (Continued)



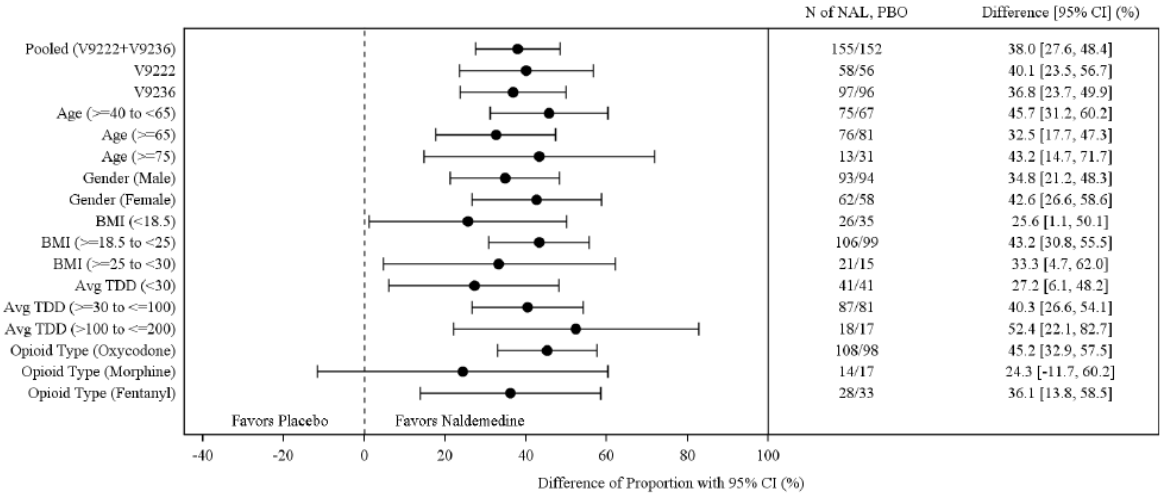
NAL : Naldemedine, PBO : Placebo

Race(American): American Indian or Alaska Native, Race(Black): Black or African American, Race(Hawaiian): Native Hawaiian or Other Pacific IslanderSource: CTD Section 5.3.5.3, Figure 14.2-1.1

Figure 9 – Difference of Proportion of SBM Responders with its 95% Confidence Intgerval (Studies V9231 and V9232), ITT Population (Continued)

Cancer studies:

The primary endpoint, proportion of SBM responders, was defined as at least 3 SBMs/week and an increase in frequency of SBM from baseline of at least 1 SBM/week during the 2-week treatment period. This was analysed according to subgroup for the individual studies V9222 and V9236, and the pool. The subgroups examined were age, gender, BMI, average TDD, and opioid type. Subjects were assigned to an opioid type if the dose of that opioid corresponded to at least 75% of the total MED during the treatment period. The resulting treatment difference with 95% CIs are presented in the figure below.



Avg TDD: Average Total Daily Dose at Baseline. Opioid type per subject was identified based on >=75% of MED

Source: CTD Section 5.3.5.3, Figure 14.2-1-2

Figure 10 – Difference of Proportion of SBM Responders with its 95% Confidence Interval (Studies V9222 and V9236), Full analysis Set

- **Responders, SBM**

Pool of V9231 and V9232: The primary endpoint was proportion of SBM responders defined as at least 3 SBMs/week with at least 1 SBM/week increase over baseline for at least 9 out of 12 weeks and at least 3 of the last 4 weeks. Treatment with naldemedine resulted in a significantly larger proportion responders than treatment with placebo (p=0.0020). The difference in proportion of responders was 16.0%.

Pool of V9222 and V9236: The primary endpoint, proportion of SBM responders, was defined as at least 3 SBMs/week and an increase in frequency of SBM from baseline of at least 1 SBM/week during the 2-week treatment period. Treatment with naldemedine resulted in a significantly larger proportion responders than treatment with placebo (p=<0.0001). The difference in proportion of responders was 38.0%.

Despite the different definitions of SBM responders, the proportions and treatment differences are generally similar across all studies:

Figure 11 – Consistency of SBM Responder Rates Across Studies

In order to better compare the proportions of SBM responders, the following post-hoc definition of SBM responders for the first 2 weeks was implemented: at least 3 SBMs/week (on average) with at least 1 SBM/week (on average) increase from baseline at both Week 1 and 2 of the treatment period.

The treatment difference for proportion of SBM responders in the first 2 weeks in the non-cancer studies were 20.8%, 21.8%, and 21.3% for V9231, V9232, and the pool respectively. For the cancer studies the treatment differences was 38.7%, 34.8%, and 36.3% for V9222, V9236, and the pool respectively.

- **Responders, CBM**

Pool of V9231 and V9232: A CSBM responder was defined as at least 3 CSBMs/week with at least 1 CSBM/week increase over baseline for at least 9 out of 12 weeks and at least 3 of the last 4 weeks. Treatment with naldemedine resulted in a significantly larger proportion responders than treatment with placebo (p<0.0001). The difference in proportion of responders was 11.9%, compared to 10.6% (V9231) and 13.3% (V9232) in the individual studies.

Pool of V9222 and V9236: A CSBM responder was defined as at least 3 CSBMs/week and an increase in frequency of CSBM from baseline of at least 1 CSBM/week during the 2-week treatment period. Treatment with naldemedine resulted in a significantly larger proportion responders than treatment with placebo (p=<0.0001). The difference in proportion of responders was 29.4%, compared to 32.3% (V9222) and 27.7% (V9236) in the individual studies.

Despite the different definitions of CSBM responders, the proportions and treatment differences are generally similar across all studies:

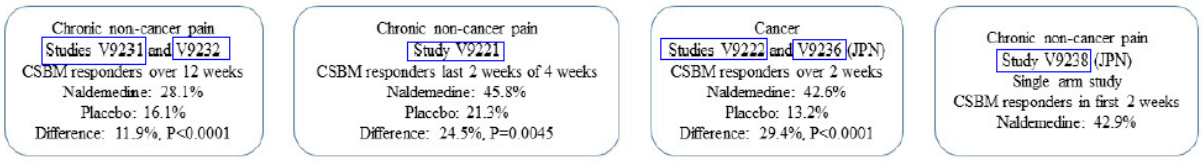
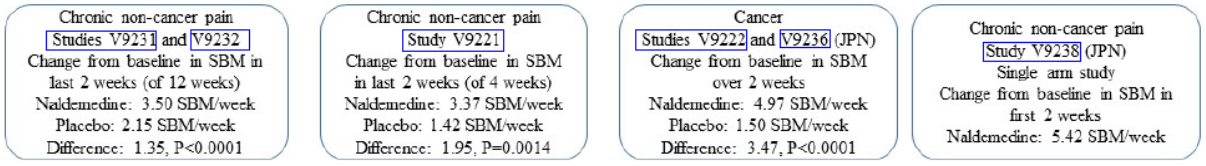


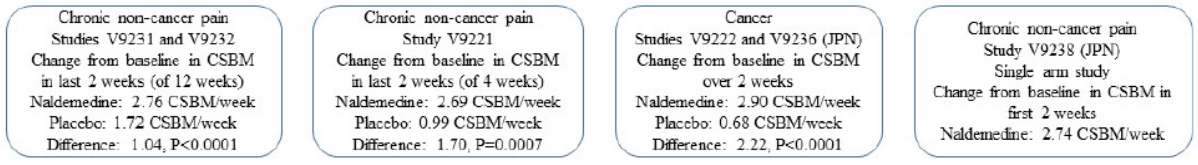
Figure 12 - Consistency of CSBM Response Rates Across Studies

- **Consistency**

The studies were of different durations, but the results in below figures show changes in SBM ranging from 3.37 to 5.42 SBM/week for naldemedine compared to 1.42 to 2.15 SBM/week for placebo. Similarly changes in CSBM ranged from 2.69 to 2.90 CSB/week for naldemedine compared to 0.68 to 1.72 CSBM/week for placebo.



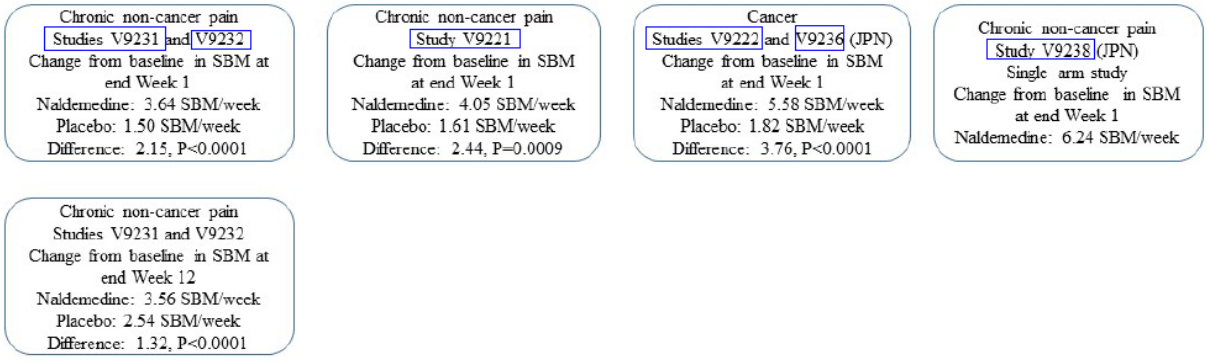
Data shown are LS means from ANCOVA in all studies except for V9238 which shows the arithmetic mean.



Data shown are LS means from ANCOVA in all studies except for V9238 which shows the arithmetic mean.

Figure 13 – Consistency of Changes from Baseline in SBM/week Across Studies

Moreover changes in frequency of SBMs from baseline to Week 1 ranged from 3.64 to 6.24 SBM/week for naldemedine compared to 1.50 to 1.81 SBM/week for placebo, see the below figure.



Data shown are LS means from MMRM in all studies except for V9238 which shows the arithmetic mean.

Figure 14 – Consistency of LS Mean Changes from Baseline in SBM/week at Week 1 (All Studies) and Week 12 (Studies V9231 and V9232)

- **Time to onset of action**

Median time to first SBM was significantly shorter for naldemedine than placebo, both in studies V9231, V9232, and the pool. The results were 16.07 vs 46.73, 18.33 vs 45.92, and 17.67 vs. 46.70 hours for V9231, V9232, and the pool respectively. Note that consistent results were found in V9221 with median times of 11.08 and 49.57 hours for naldemedine and placebo.

Median time to first SBM was significantly shorter for naldemedine than placebo, both in studies V9222, V9236, and the pool. The results were 4.33 vs 45.43, 4.67 vs 26.58, and 4.42 vs. 30.88 hours for V9231, V9232, and the pool respectively.

- **Quality of life**

Non-cancer pain: PAC-SYM and PAC-QOL scores were assessed at baseline, and at Weeks 2, 4, and 12 in V9231 and V9232, and in V9235 at Weeks 2, 12, 24, 36, and 52. Changes in the overall score for PAC-SYM from baseline to Weeks 2 and 12 were similar for the three studies and all statistically significant improved for naldemedine compared to placebo. The treatment effects ranged from -0.25 to -0.35. For study V9235 statistically significant improvements for naldemedine were also found at all later time points. The results for each domain of the PAC-SYM were generally similar to the overall score, with the exception that the abdominal symptoms domain was not significantly improved in study V9232, there was only a numeric improvement. Changes in the overall score for PAC-QOL from baseline to Weeks 2 and 12 were similar for the three studies and all statistically significant improved for naldemedine compared to placebo. The treatment effects ranged from -0.26 to -0.40. The results for each domain of the PAC-SYM were generally similar to the overall score, with the exception that for the psychosocial discomfort domain there was only a numeric improvement in studies V9231 and V9232, but it was not statistical significant. For study V9235 statistically significant improvements for naldemedine were also found at all later time points.

Study V9236 (cancer): For the PAC-SYM overall scores as well as for all domain scores, apart from the stool symptom score, there was no difference in change from baseline between naldemedine and placebo. The change from baseline in PAC-SYM stool symptoms score was more improved for naldemedine than for placebo both at Visit 4 and at last observation. For the PAC-QOL overall scores as well as for all domain scores, apart from the dissatisfaction score, there was no difference in change from baseline between naldemedine and placebo. The change from baseline in PAC-QOL dissatisfaction score was more improved for naldemedine than for placebo but only at Visit 4.

- **LIR/non-LIR subgroup**

- **Responders**

Pool of V9231 and V9232: The primary endpoint, proportion of SBM responders during the treatment period, was defined as at least 3 SBMs/week with at least 1 SBM/week increase over baseline for at least 9 out of 12 weeks and at least 3 of the last 4 weeks. The proportion of SBM responders was significantly higher for naldemedine than for placebo for both the LIR and non-LIR subgroups. The treatment effects were 16.2% and 15.6% for the LIR and the non-LIR subgroups respectively. For CSBM responders, defined analogously, the proportion was significantly higher for naldemedine than for placebo for both the LIR and non-LIR subgroups. The treatment effects were 10.5% and 15.1% for the LIR and the non-LIR subgroups respectively.

An SBM responders during the first 4 weeks was defined as at least 3 SBMs/week (on average) with at least 1 SBM/week (on average) increase over baseline in at least 3 of the 4 weeks. The proportion of SBM responders in the first 4 weeks was significantly higher for naldemedine than for placebo for both the LIR

and non-LIR subgroups. The treatment effects were 19.3% and 18.4% for the LIR and the non-LIR subgroups respectively.

V9221: The proportion of SBM responders during the first 2 weeks was defined as at least 3 SBMs/week (on average) with at least 1 SBM/week (on average) increase over baseline at both Week 1 and Week 2 of the treatment period. The proportion of SBM responders was significantly higher for naldemedine than for placebo for both the LIR and non-LIR subgroups. The treatment effects were 25.0% and 35.0% for the LIR and the non-LIR subgroups respectively.

An SBM responder during the first 4 weeks was defined as at least 3 SBMs/week with at least 1 SBM/week increase over baseline in at least 3 of the 4 weeks. The proportion of SBM responders in the first 4 weeks was numerically higher for naldemedine than for placebo for both the LIR and non-LIR subgroups. The treatment effects were 30.7% and 28.8% for the LIR and the non-LIR subgroups respectively, but only statistically significant for the LIR subgroup, most likely due to the small size of the non-LIR subgroup.

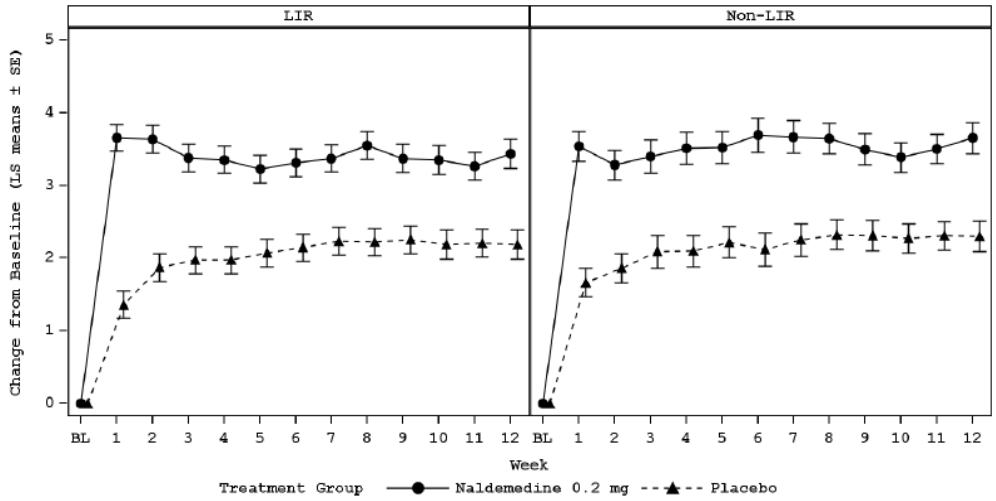
Pool of V9222 and V9236: The proportion of SBM responders during the first 2 weeks was defined as at least 3 SBMs/week (on average) with at least 1 SBM/week (on average) increase over baseline at both Week 1 and Week 2 of the treatment period. The proportion of SBM responders was significantly higher for naldemedine than for placebo for both the LIR and non-LIR subgroups. The treatment effects were 36.1% and 41.8% for the LIR and the non-LIR subgroups respectively.

Pool of V9231 and V9232: In order to more directly compare with the results in the cancer trials, the proportion of SBM responders during the first 2 weeks was defined as at least 3 SBMs/week (on average) with at least 1 SBM/week (on average) increase over baseline at both Week 1 and Week 2 of the treatment period. The proportion of SBM responders was significantly higher for naldemedine than for placebo for both the LIR and non-LIR subgroups. The treatment effects were 23.1% and 18.8% for the LIR and the non-LIR subgroups respectively.

- **Other endpoints**
- **Pool of V9231 and V9232**

Change in frequency of SBMs:

A greater change in the frequency of SBMs per week from baseline to the last 2 weeks of treatment for naldemedine than placebo was found for both subgroups. Treatment differences were 1.28 and 1.39 SBMs for the LIR and the non-LIR subgroups, both statistically significant. Similarly a greater change in the frequency of SBMs per week from baseline to Week 1 of treatment for naldemedine than placebo was found for both subgroups. Treatment differences were 2.28 and 1.90 SBMs for the LIR and the non-LIR subgroups, all statistically significant. The MMRM analysis showed statistically significant treatment differences (of at least 0.82 SBMs) at all time points for both the LIR and the non-LIR subgroup.

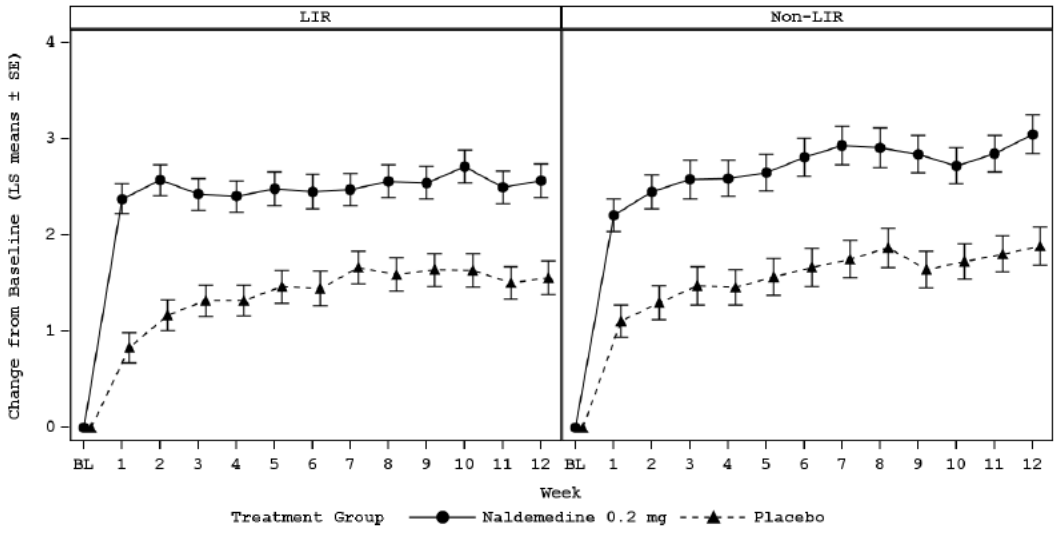


Baseline (BL) was 14 consecutive calendar day qualifying period during the screening period.
Source: CTD Section 5.3.5.3, Figure 14.2-3.1-1a

Figure 15 – Change in the Frequency of SBMs/week from Baseline to Each Week by LIR/Non-LIR Subgroups: LS Mean ± SE (Studies V9231 and V9232), ITT Population

Change in frequency of CSBMs:

A greater change in the frequency of CSBMs per week from baseline to the last 2 weeks of treatment for naldemedine than placebo was found for both subgroups. Treatment differences were 1.06 and 1.17 CSBMs for the LIR and the non-LIR subgroups, both statistically significant. The MMRM analysis showed statistically significant treatment differences (of at least 1.01 CSBMs) at all time points for both the LIR and the non-LIR subgroup.



Baseline (BL) was 14 consecutive calendar day qualifying period during the screening period
Source: CTD Section 5.3.5.3, Figure 14.2-3.2-1a

Figure 16 – Change in the Frequency of CSBMs/week from Baseline to Each Week by LIR/Non-LIR Subgroups: LS Mean ± SE (Studies V9231 and V9232), ITT Population

- **Durability, Pool of V9231 and V9232, and V9235**

Change in frequency of BMs:

For the change in frequency of BM the MMRM analysis showed statistically significant treatment differences (of at least 1.03 BMs) at Week 12 for both the pool of V9231 and V9232 and the study V9235 for both the LIR and the non-LIR subgroups. For Weeks 24, 36, and 52, study V9235 only showed a numerically favourable treatment difference, which was no longer statistically significant. Nothing indicated a different treatment effect in the LIR and non-LIR subgroups in the long-term study.

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials			
Non Controlled Trials			

Supportive studies

There are three supportive studies. All supportive studies (V9237, V9238 and V9239) were single-arm, open-label studies conducted in Japan. Study V9237 was conducted as a follow-up study in cancer patients who had completed participation in Study V9236; treatment period of this study was 12 weeks and 131 patients were enrolled. Studies V9238 and V9239 were conducted over 48 weeks in non-cancer patients and included 40 and 10 patients, respectively. In all three supportive studies, patients were treated with naldemedine 0.2 mg once daily and use of regular and rescue laxatives was permitted.

The primary objective in all three supportive studies was to evaluate the long-term safety of naldemedine in patients with chronic (non-)cancer pain and OIC, and efficacy was included as a secondary objective. Efficacy variables included change in (C)SBM frequency, proportion of (C)SBM responders and change in and proportion of PAC-SYM and PAC-QOL (responders).

All patients included in the supportive studies were Asian and mean weight in the three studies was 53-55 kg. Mean daily dose of opioids (as equivalent oral morphine dose) was 45-75 mg, median daily opioid dose was 45-60 mg and the range across all three studies was 5-720 mg daily. Among all three studies, 27 (14.75%) patients were treated with a daily opioid dose ≥120 mg and 47 (25.68%) patients were treated with a daily dose <30 mg. Use of regular- (and rescue-) laxatives (other than naldemedine) during the study period was 70-90%.

In Study V9237, treatment with naldemedine improved PAC-SYM and PAC-QOL scores compared to baseline. At end-of-trial, mean change from baseline was -0.39 (±0.54) for PAC-SYM score however, the effect had declined from the beginning of the extension study (V9237), where the PAC-SYM score difference from baseline was -0.91 (±0.56). At end-of-trial, the proportions of PAC-SYM and PAC-QOL responders were 18.5% and 35.3%, respectively.

In Study V9238, the proportion of SBM responders was 85.7% at Week 1 and 76.2% at Week 2 [LOCF] was noticeable higher compared with the results from the 12 Weeks pivotal non-cancer studies (47.6-52.5%, Studies V9231 and V9232) and also a bit higher than the results from the 2 Weeks pivotal cancer studies (71.1–77.6%, Studies V9236 and V9222). The overall change from baseline in PAC-SYM was -0.92 (-0.81 for LOCF) after the full treatment period (48 weeks). The results were stable throughout the observation period (from Week 6) and statistically significant ($p<0.0001$) but somewhat lower than

the results in the pivotal studies (i.e. -1.01 in Study V9232, -1.23 in Study V9235 and-1.25 in Study V9236). Similar results are found for PAC-QOL (-1.03 in the present Study V9237 and -1.08 and -1.26 in Studies V9235 and V9236, respectively).

In Study 9239, the proportion of SBM and CSBM responders was 90% and 50%, respectively after 2 weeks treatment. The proportion of (C)SBM responders was not evaluated again during the 48 treatment weeks. With regards to PAC-SYM and PAC-QOL score, at end of study (48 weeks treatment), the overall change from baseline in PAC-SYM was -0.94 (-0.89 for LOCF). The results for PAC-SYM and PAC-QOL were stable throughout the observation period (from Week 6) and statistically significant ($p<0.0001$ for PAC-SYM and $p<0.002$ for PAC-QOL).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Dose-finding:

Dose-finding was explored in three phase II studies, two in non-cancer patients, studies V9214 and V9221, and one study in cancer patients, study V9222. All studies were randomised, double-blind, placebo-controlled studies. Study V9214 was a small study evaluating 6 dose levels (0.01, 0.03, 0.1, 0.3, 1 and 3 mg) with the primary efficacy change from baseline to 24 hours post-dose in the number of SBMs. Study V9221 was subsequently performed based on the results from study V9214 testing doses of naldemedine 0.1 mg, 0.2 mg, or 0.4 mg QD with the primary endpoint, change in the frequency of SBMs/week from baseline to the last 2 weeks of the treatment period. Responder rates were part of the secondary endpoints. In study V9222, the same dose range was tested with the primary endpoint change in the frequency of SBMs/week from baseline. In this study, responder rates were also part of the secondary endpoint. The study designs as well as the choice of doses in these studies are reasonable.

Pivotal studies:

All 4 pivotal studies, 3 in non-cancer patients (V9231, V9232, and V9235) and 1 in cancer patients (V9236) were randomised double-blind studies comparing treatment with naldemedine to treatment with placebo. The trials used the to-be recommended dose of 0.2 mg naldemedine QD, and the study designs are in general in accordance with requirements in current EMA Guidelines (including EMA Guideline on the evaluation of medicinal products for the treatment of chronic constipation (including opioid induced constipation) and for bowel cleansing [EMA/CPMP/336243/2013]). Duration of treatment period and follow-up period are also in accordance with current guidelines, apart from trial V9236, where the treatment duration was only 2 weeks compared to the recommended 4 weeks. The trial was, however, designed prior to the publishing of the guideline and as such is considered appropriate. All studies apart from V9236 conducted in Japan, were multi-national including study centres in Europe and the US as well as Asia Pacific. All 4 pivotal studies used comparison to placebo, which is in line with the guideline, although the guideline also suggests consideration of inclusion of an active comparator. The choice of using placebo is nevertheless accepted even though methylnaltrexone (Relistor®, as subcutaneous injection) was approved in 2008.

All trials used appropriate inclusion criteria in accordance with the guideline ensuring that the opioid induced constipation is as stable as possible and that change in SBM are not due to changes in opioid therapy.

Trials V9231 and V9232 investigated the effect of naldemedine as monotherapy and discontinued laxative use at screening, whereas in trials V9235 and V9236 subjects using a stable laxatives regimen at screening would continue this regimen throughout the trial, and hence investigated the effect of

naldemedine both as add-on to laxatives and as monotherapy. In trial V9235, the subgroup of subjects on stable laxative regimen/subjects not on a stable laxative regimen was analysed resulting in similar results. A similar subgroup analysis was performed in V9236 showing effectiveness of naldemedine in both settings.

For trials V9231 and V9232, the primary endpoint (proportion of responders) is in accordance with the guideline, and the secondary and exploratory endpoints constitute a comprehensive evaluation of supportive evidence. Trial V9235 is a long-term safety study with efficacy as secondary endpoint. The primary endpoint for trial V9236 was proportion of responders, although this according to the guideline should only be a secondary evaluation due to the reduction in power. Also in this study the secondary endpoints constitute a comprehensive evaluation of supportive evidence.

The methods for randomisation are considered adequate, although in trial V9235 stratification according to stable laxative regimen was not performed.

In trials V9231 and V9232, a pre-specified fixed sequence approach to control the family wise type 1 error rate for the testing of secondary efficacy endpoints is used, which is supported. For trials V9235 and V9236 there is no multiplicity adjustment for secondary endpoints, hence the results of those analyses are considered exploratory only.

The method for computing number of SBMs per week varies by study, which complicates comparisons, however this is acceptable. In trials V9231 and V9232, a total of at least 4 days of diary entries related to defecation a week is necessary, otherwise the week will be considered non-evaluable. This choice seems arbitrary and is questioned, however repeating the analysis with choosing 3 or 5 days instead of 4 days did not change the result.

The frequency of SBMs (BMs) per week was defined as:

- Trials V9231 and V9232: 7*(total frequency of SBMs in the week)/(Number of days of observation related to defecation in the week)
- Trial V9235: 7*(total frequency of BMs for each selected visit)/(Number of days of observation related to defecation for each selected visit)
- Trial V9236: 7*(total frequency of SBMs during the treatment period)/(Number of days in the treatment period)

The first two definitions implicitly assume that days with diary entry related to defecation are representative of days without diary entry related to defecation. As it seems more likely that the diary is filled in if there is a BM to register, this assumption may not be valid. However, in subsequent analyses where missing entries were regarded as 0 (bowel movements) (and the corresponding week not considered non-evaluable in spite of missing entries) naldemedine was consistently statistically superior to placebo. Similar results were obtained in a number of sensitivity analyses applying a range of different definitions of how to handle missing values (including a worst case scenario where weeks which had any number of missing entries of bowel movements were regarded as a non-response week) demonstrating the robustness of results.

Several analyses are performed comparing changes between groups using an ANCOVA, but there is no adjustment for baseline. Additional analyses including baseline as a covariate have been provided with unchanged results.

Rizmoic was chosen for a routine GCP inspection. At the inspection, critical GCP violations were recorded for study V9235 necessitating exclusion of data from these sites. The overall results were not significantly affected by the exclusion of data. In addition, it was noted that patients did not have the possibility to

correct the electronic diary regarding the number of spontaneous bowl movements. This was considered a critical GCP finding. The applicant was therefore requested to complete and submit a re-analysis of efficacy data (of studies V9231, V9232 and V9235) including primary as well as secondary efficacy endpoint following correction of data based on the available source documentation at participating sites (including un-submitted and un-generated DCFs).

Upon collection of data correction forms the applicant performed the requested re-analyses based on available source documentation at the participating sites and previously submitted but denied data change requests. No data corrections impacted the primary and secondary efficacy endpoints in Study V9231 and so no re-analyses were required for this study. Re-analysis of the primary and secondary endpoints in Study V9232 showed very similar or identical results to the original analyses. Similarly, no changes were seen in the sensitivity analyses for this study. Results for the secondary efficacy endpoints in Study V9235 using the updated database (there was no primary efficacy endpoint in this study) were very similar to the original analyses with no clinically important differences seen between the analyses. These results show that inclusion of denied, unsubmitted, and ungenerated data clarification forms (DCFs) for electronic patient outcomes data has not altered the positive benefit:risk assessment seen for naldemedine based on the original analyses.

Supportive studies:

All three supportive studies (V9237, V9238 and V9239) were designed as single-arm, open-label studies conducted in Japan. The design of the trial as well as the limited number of included patients (total 181 in all three studies) limit firm conclusions and the trials must therefore be considered to be only supportive for the pivotal studies. In all three supportive studies, patients were treated with naldemedine 0.2 mg once daily. The dose could be temporary reduced (to 0.1 mg) or treatment could be temporary discontinued in case of the patients' QOL was reduced due to GI AE.

Efficacy data and additional analyses

Dose-finding:

In study V9214, 0.3 mg was the minimum effective dose in patients treated with at least 90 mg morphine-equivalent dose (MED) per day The primary endpoint was not adjusted for any baseline imbalance as regards to baseline opioid dose. Study V9221, exploring if the dose found to be the minimally effective dose in study V9214 (0.3 mg) would be the most appropriate dose, found that the 0.2 mg and the 0.4 mg dose differed statistically and clinically relevant from both placebo and the 0.1 mg dose, but between the 0.2 mg and the 0.4 mg doses there was no clinically or statistically relevant difference, although a numerically better efficacy was observed for all endpoint for the 0.4 mg dose. However, the 0.4 mg dose was associated with a higher number of adverse events as compared to the 0.2 mg dose. It thus seem that, based on this study, that the 0.2 mg dose is the optimal dose, but it is noted that mean dose of opioid analgesic was "only" 120-146 mg MED. This could question whether 0.2 mg naldemedine is the optimal dose in patients who are treated with higher doses. Higher doses than e.g. 150 mg MED are not uncommon in European cancer and non-cancer patients**.** Study V9222 found a clear dose-response with the 0.4 mg dose resulting in both clinically relevant and statistically higher number of SBM as compared to both placebo, the 0.1 mg and the 0.2 mg dose. It is however also noted that with the 0.4 mg dose the mean was 8.35 SBM/week with an SD of 8.35. This means that some of these patients had more than one SBM per day. In fact, 52% in the 0.4 g dose group had an AE of diarrhoea vs. 40% in the 0.2 mg dose group and approximately 25% and 27% in the 0.1 mg dose group and placebo group, respectively. The 0.1 mg dose was just statistically significant superior to placebo and 0.2 mg was numerically more efficient than the 0.1 mg dose. In this study, the most appropriate dose is 0.2 mg. However, this study vs. study V9221 in non-cancer patients, the dose-response is much more evident and

the number of responders and change from baseline in BM is higher. Considering the pharmacological mode of action of naldemedine (mu-receptor antagonist), the efficacy of naldemidine must be considered clearly dependent on the amount of opioid used. Even though comparison across studies should always be done with caution, it is striking that there is clearly a better effect in particular for the 0.4 mg dose in the cancer patients in study V9222 as compared to the non-cancer study V9214. The dose-response is also much clearer in study V9222. This could be explained by the overall lower mean opioid use in study V9222 and the relatively large number of patients who had a baseline opioid use of less than 50 mg. This questions if the chosen dose of 0.2 mg is sufficiently effective in patients with a high daily opioid use. However, considering also the results from the pivotal studies the 0.2 mg naldemedine dose appear to be the most optimal dose for the treatment opioid induced constipation in patients treated with up to 400 mg MED and the SmPC informs the prescriber adequately that about the limited experience in patients treated with opioid pain medicinal product(s) at daily doses of more than the equivalent of 400 mg of morphine.

Pivotal studies

For all trials, the recruitment and participant flow are adequately described. The main reasons for discontinuation were subject withdrawal and adverse events (mainly in the gastrointestinal SOC), which appeared more common in the naldemedine group.

The protocol amendments are generally well described in the clinical study reports.

For all trials, the patients' characteristics were generally well balanced between the two treatment groups, and generally the study populations seemed to reflect the general population in which naldemedine is intended to be used. However, the baseline mean opioid dose (in oral morphine equivalent doses) is considered relatively low in the pivotal non-cancer studies (118-140 mg) and also in the cancer studies (57-69 mg) questioning the efficacy of naldemedine in patients who are treated with higher opioid doses. It is sufficiently reflected in the SmPC that there is limited experience in patients treated with more than 400 mg morphine-equivalent daily doses.

For trials V9231, V9232 and V9235 the ITT population consisted of all subjects. However, it is noted that there was double enrolment at for three patients at different sites. These were withdrawn from the study.

SBM/CSBM responders:

Trials V9231, V9232, and the pool (non-cancer):

SBM responder during the 12-week treatment period was defined as at least 3 SBMs/week with at least 1 SBM/week increase over baseline for at least 9 out of 12 weeks and at least 3 of the last 4 weeks, and CSBM responders were defined similarly.

- The treatment difference for naldemedine relative to placebo was 13%, 18.9%, and 16.0% respectively for proportion of SBM responders, and 10.6%, 13.3%, and 11.9% for proportion of CSBM responders, all statistically significant.

Trials V9222, V9236, and the pool (cancer):

SBM responder during the 2-week treatment period was defined as at least 3 SBMs/week with at least 1 SBM/week increase over baseline during the treatment period, and CSBM responders were defined similarly.

- The treatment difference for naldemedine relative to placebo was 40.1%, 36.8%, and 38.0% respectively for proportion of SBM responders, and 32.3%, 27.7%, and 29.4% for proportion of CSBM responders, all statistically significant.

As seen, the treatment effects on both SBM and CSBM responders are 2-3 fold higher in the cancer studies than in the non-cancer studies.

In order to better compare the proportions of SBM responders between trials, the following common post-hoc definition of SBM responders for the first 2 weeks was implemented: at least 3 SBMs/week (on average) with at least 1 SBM/week (on average) increase from baseline at both Week 1 and 2 of the treatment period.

- The treatment difference for proportion of SBM responders in the first 2 weeks in the non-cancer studies was 20.8%, 21.8%, and 21.3% for V9231, V9232, and the pool respectively. For the cancer studies the treatment difference was 38.7%, 34.8%, and 36.3% for V9222, V9236, and the pool respectively.

Subgroup analyses:

In the non-cancer studies, subgroup analysis for the primary endpoint showed no difference as regards to differences in age, gender, BMI, region, opioid dose strata, average TDD, and eGFR at baseline. It is reassuring that patients who are treated with MED higher than 200 mg show convincing treatment effect of naldemedine relative to placebo, although it is noted that only few patients received more than 400 mg MED. In addition there is limited experience in patients aged 75 years or older. This is reflected in the SmPC and added to the RMP as missing information.

Patients treated with partial agonists such as buprenorphine were not included in the studies. It is possible that naldemedine might not be as effective in treating opioid induced obstipation caused by a partial opioid agonist. It is reflected in the SmPC that there is no experience for the treatment of constipation induced by partial opioid my-receptor agonists.

In the Black/African American subgroup of patients the response in the naldemedine arm compared to placebo overall is non-existing, mainly because of high placebo response in both pivotal trials and an absolute lack of efficacy of naldemedine in this patient subgroup in trial V9132.

Similarly for the cancer studies the primary endpoint was analysed according to subgroup for the individual studies V9222 and V9236, and the pool. The subgroups examined were age, gender, BMI, average TDD, and opioid type. Generally, the subgroups examined showed similar effects of naldemedine relative to placebo supporting that the treatment effect can be expected not to vary by subgroup. Only the two groups of average TDD (>30 to ≤100) and (>100 to ≤ 200) had a size sufficient large enough for meaningful comparisons. Thus the study gives no information about subjects receiving high opioid doses.

There is no/limited data in this cancer patient group for patients who received very high doses of opioid. Moreover as naldemedine is likely not to be a non-competitive antagonist, there will be a ceiling effect as to when the 0.2 mg dose no longer is sufficiently effective. There are only sufficient clinical data for patients treated with up to around 400 mg MED. For doses higher than that the effect is not clear. This is sufficiently reflected in the SmPC.

Other efficacy endpoints:

In trials V9231 and V9232, all four secondary endpoints were confirmed in the hierarchical testing, i.e. treatment with naldemedine resulted in a statistical significant higher increase in the frequency of SBMs

per week from baseline to the last 2 weeks of treatment and from baseline to Week 1 both relative to placebo, as well as a statistical significant higher increase in the frequency of CSBMs respectively SBMs without straining per week from baseline to the last 2 weeks of treatment relative to placebo. Thus the effect of treatment is already seen in Week 1 for SBMs, and is seen in the last 2 weeks for both SBMs, CSBMs, and SBMs without straining. There was no difference in use of rescue laxatives between the groups, so the effect seen on the primary and secondary endpoints is not caused by that. In addition it is worth noting that both the pain score and the opioid dose remained stable from baseline throughout the study for both treatment groups indicating that naldemedine does not cross the BBB in a clinically relevant degree.

Generally, the secondary/exploratory efficacy results support the results on responder rates by consistently showing better results for naldemedine compared to placebo in changes in frequency of SBM/CSBM/SBMs without straining/SBMs with BSS of 3 or 4.

The results on time to onset of action consistently show earlier effect for naldemedine than placebo both for cancer and non-cancer trials in support of the primary and other secondary efficacy endpoints.

PAC-SYM and PAC-QOL questionnaires are used to assess the patient's experience on constipation-related symptoms and quality of life and may add clinical relevance to the observed treatment effects. The PAC-QOL questionnaire is a validated questionnaire with which a treatment response can be measured from a patient's perspective and experience, which is considered clinically relevant in case an improvement of ≥1 point is reported. To assess the effect size of response, the number of PAC-QOL responders reporting an improvement of ≥1 versus baseline in treatment and placebo arms should be compared. In present study, average changes were reported per treatment group which indicates a numerical change in scores between treatment groups but which does not allow for an evaluation of the clinically relevant benefit triggered by treatment in individual patients. In line with above, PAC-SYM scores can be clinically relevant if properly reported, i.e. as a responder rate. A change in baseline in PAC-SYM score of 0.8 points is considered to reflect a clinically relevant change in an individual patient. To allow for an appreciation of the PAC-SYM and PAC-QOL scores, the applicant has also reported responder rates compared to baseline and associated statistics for PAC-SYM and for the PAC-QOL domain dissatisfaction.

For PAC-SYM and PAC-QOL, the scores were generally significantly improved for naldemedine compared to placebo for the non-cancer studies in support of the primary and secondary efficacy endpoints. For the cancer studies though, there was generally no difference between the treatment groups with respect to the PAC-SYM and PAC-QOL scores, even though the efficacy in cancer studies appears to be better than in the non-cancer studies. The same was true when the responder rates were analysed. With low baseline values for the questionnaires, it seems that constipation has little influence on the quality of life for cancer patients, and naldemedine does not have a significant effect on quality of life compared to placebo. This is probably as expected. However, it is reassuring that in the non-cancer patient studies the effect of naldemedine also translates into an increase in quality of life.

An early onset of the effect of naldemedine on OIC was seen, and the effect was sustained through 12 weeks. Rescue laxative use was either similar in the groups or more prominent in the placebo group, hence can only be diluting the result. In the long-term study V9235, the effect of change from baseline in BMs was durable for up to 52 weeks. As similar change from baseline results for BM were seen at week 12 for V9231 and V9232 as for V9235, this suggests that the treatment effect could be sustainable for up to 52 weeks. Moreover, similar efficacy results are shown both for subjects on a stable laxative regimen and for subjects not on a stable laxative regimen, however less convincing in the last subgroup.

The treatment effect found in the cancer studies was substantially higher than the treatment effect found in the non-cancer studies for all efficacy parameters, apart from PAC-SYM and PAC-QOL. However, the

cancer study was performed in Japanese subjects only, and only included subjects with quite low opioid doses. The difference in treatment effect in the cancer vs. the non-cancer studies is most likely due to the relatively low opioid doses used in the cancer studies.

LIR and non-LIR subgroups:

According to the guideline, if a general claim without specifying the "line of therapy" is aimed at, the studies should be powered such that a statistically significant effect is shown in both subgroups (first line and those with previously unsuccessful treatment).

The laxative inadequate response (LIR) and non-LIR subgroups were defined post-hoc for the trials V9231, V9232, V9221, V9235, V9222, and V9236. However, the definition of the LIR subgroup is not in accordance with the guideline, which states that a subject *"should have confirmed insufficient response to laxative treatment with at least two drug substances belonging to different classes used in the treatment of constipation by history taking"*, however it is reasonable to conclude that naldemedine will be effective in LIR as well as non-LIR groups of patients. The non-LIR subgroup in studies V9231 and V9232 cannot be considered a first line, laxative treatment-naïve population, thus two additional groups of "virtually laxative naïve" subjects have been examined. The *laxative naïve to first dose subgroup* consisted of subjects who 1) received no laxatives from 90 days prior to 1 day before the first dose, and 2) used only rescue laxatives after the first dose or did not take any laxatives after the first dose. This group consisted of only 72 subjects, 35 treated with naldemedine, and 37 treated with placebo. The *laxative naïve to screening subgroup* consisted of subjects who 1) received no laxatives in the 90 days prior to screening, and 2) used only rescue laxatives during screening and after Visit 1, or did not take any laxatives. This group consisted of 209 subjects treated with naldemedine, and 216 subjects treated with placebo. The results for laxative naïve to first dose subgroup and laxative naïve to screening subgroup were treatment differences versus placebo of 13.6% respectively 17.3% for the pool of studies V9231 and V9232. For the laxative naïve to first dose subgroup with only 72 subjects, the treatment difference was not statistically significant, in contrast to the laxative naïve to screening subgroup. However, both groups show clinically relevant treatment differences of naldemedine relative to placebo, and the fact that the effect is not statistically significant for the laxative naïve to first dose subgroup is likely due to the small group size. Thus, generally the results in the laxative naïve subgroups are in line with the overall results showing superior efficacy of naldemedine compared to placebo at week 12. Demonstration of efficacy in 12 weeks is in accordance with guidelines. However, the effect seems to diminish beyond 12 weeks treatment in the laxative naïve subgroups as compared to placebo. This could be a chance finding as the placebo response was high. Regardless, strictly laxative naïve patients have not been studied and thus the indication is restricted to include patients who have previously used laxatives. It is surprising that the sizes of the LIR groups are very different for trials V9231 and V9232 given that the trials were of identical design, however no reason have been found and it is probably just due to chance

The LIR and the non-LIR subgroups were defined post-hoc and the individual trials were not powered to show treatment effect separately in these subgroups. However, for the pool of the two identically designed trials, V9231 and V9232, the subgroups were actually large enough to consistently show similar statistically significant treatment differences in responder proportions in the LIR and the non-LIR subgroups.

For the pool of trials V9231 and V9232, the secondary efficacy results consistently show very similar treatment effects in the LIR and non-LIR subgroups. Thus it has been demonstrated that for the non-cancer trials the efficacy in the LIR and the non-LIR subgroups appears to be comparable. For the cancer trial, V9236, the secondary efficacy results also consistently show similar very similar treatment effects, thus are in support of the primary endpoint showing efficacy of naldemedine in both the LIR and the non-LIR subgroups.

Supportive studies

All patients included in the supportive studies were Asian and mean weight in the three studies was 53-55 kg; thus considerable lower than the average European population. Consequently, in the three studies, mean daily MEDe of opioids was also lower; 45-75 mg (median daily opioid dose 45-60 mg) and the range across all three studies was 5-720 mg daily. Among all three studies, 27 (14.75%) patients were treated with a daily MED ≥120 mg but of note, 47 (25.68%) patients were treated with a daily dose MED <30 mg. These opioid doses are considerable lower than what can be expected to be used among European cancer and non-cancer chronic pain patients.

Use of regular- (and rescue-) laxatives (other than naldemedine) during the study period was 70-90%.

Study V9237 was an extension study of Study V9236. Patients completing Study V9236 were to be continued into Study V9237.

In Study V9237, treatment with naldemedine improved PAC-SYM and PAC-QOL scores compared to baseline. At end-of-trial, mean change from baseline was -0.39 (±0.54) for PAC-SYM score however, the effect had declined from the beginning of the extension study (V9237), where the PAC-SYM score difference from baseline was -0.91 (±0.56). This could indicate that the effect diminishes over time though this has not been observed in the long-term non-cancer studies. Change from baseline in PAC-QOL remained stable throughout the study and was -0.41 (±0.54) at end-of-trial. At end-of-trial, the proportions of PAC-SYM and PAC-QOL responders were 18.5% and 35.3%, respectively. A possible reason for the modest improvement is due to the low baseline scores leaving little room for improvement.

In Study V9238, the proportion of SBM responders (85.7% at Week 1 and 76.2% at Week 2 [LOCF]) were noticeable higher compared with the results from the 12 Weeks pivotal non-cancer studies (47.6-52.5%, Studies V9231 and V9232) and also a bit higher than the results from the 2 Weeks pivotal cancer studies (71.1–77.6%, Studies V9236 and V9222). The overall change from baseline in PAC-SYM and PAC-QOL were stable throughout the observation period (from Week 6) and statistically significant ($p<0.0001$) but somewhat lower than the results in the pivotal studies.

In Study 9239, the proportion of SBM and CSBM responders (90% [SBM] 50-60% [CSBM], respectively) was higher than observed in the 2 Weeks cancer studies (77.6-71.1%, Studies V9222 and V9236) and substantially higher than the results from the 12 Weeks pivotal non-cancer studies (47.6-52.5%, Studies V9231 and V9232). With regards to PAC-SYM and PAC-QOL score, at end of study (48 weeks treatment), the overall change from baseline were stable throughout the observation period (from Week 6), statistically significant ($p<0.0001$ for PAC-SYM and $p<0.002$ for PAC-QOL) and supports the results obtained in the pivotal studies.

2.5.4. Conclusions on the clinical efficacy

In the non-cancer studies, naldemedine has been demonstrated to be more effective than placebo in the treatment of opioid induced constipation in subjects with chronic pain. In the cancer study, naldemedine was also demonstrated to be more effective than placebo in the treatment of opioid induced constipation in subjects with cancer pain, even with a higher treatment effect. However, there is limited information regarding patients treated with > 400 mg morphine equivalent, which is reflected in the SmPC. Furthermore, in order to get the general claim “treatment of opioid-induced constipation” effect must be demonstrated both in the inadequate response to laxatives (LIR) and non-LIR subgroups as well as in patients not previously treated with laxatives. The post-hoc defined non-LIR group was not according to guideline, but in addition the treatment effect in two groups of virtually laxative naïve subjects was also presented with similar results. Overall efficacy and safety of naldemedine has been demonstrated by showing consistent results in both LIR and non-LIR subgroups based on varying definitions of non-LIR.

Generally, the results in the laxative naïve subgroups are in line with the overall results showing superior efficacy of naldemedine compared to placebo at week 12. However, it is noted that strictly laxative naïve patients have not been studied. Thus the indication is restricted to patients who have used laxative previously.

2.6. Clinical safety

Patient exposure

A clinical programme has been completed comprised of 22 studies: 12 Phase 1 studies; 1 Phase 2a single-dose proof-of-concept study in subjects with chronic non-cancer pain, opioid-induced bowel dysfunction (OBD), and opioid physical dependence; 6 Phase 2 and Phase 3 studies in subjects with chronic non-cancer pain and OIC; and 3 Phase 2 and Phase 3 studies in subjects with cancer and OIC. Safety data were assessed in all studies. Please refer to the tabular overview of clinical studies for a further description of the studies.

Across the naldemedine clinical development programme, 2139 subjects were exposed to naldemedine, including 351 healthy subjects or subjects with varying degrees of renal or hepatic impairment, 1452 subjects with chronic non-cancer pain and OIC, and 336 subjects with cancer and OIC. Of these, 1969 subjects received naldemedine at a dose of at least 0.2 mg (325 healthy subjects or subjects with varying degrees of renal or hepatic impairment, 1364 subjects with chronic non-cancer pain and OIC, and 280 subjects with cancer and OIC).

Across the naldemedine Phase 2 and Phase 3 clinical development programme, 1644 subjects with OIC were exposed to daily doses of naldemedine ≥ 0.2 mg, 1364 subjects with chronic non-cancer pain and OIC and 280 with cancer and OIC.

Subject disposition

Non-cancer and OIC

Table 20 Subject Disposition in Treatment Period (Global Placebo-controlled Phase 3 up to First 12 Weeks) – All Randomised Subjects

	V9231		V9232		V9235		Overall	
	NAL 0.2 mg N=274 n (%)	PBO N=273 n (%)	NAL 0.2 mg N=277 n (%)	PBO N=276 n (%)	NAL 0.2 mg N=623 n (%)	PBO N=623 n (%)	NAL 0.2 mg N=1174 n (%)	PBO N=1172 n (%)
Subjects Completed	240 (87.6)	244 (89.4)	240 (86.6)	236 (85.5)	561 (90.0)	556 (89.2)	1041 (88.7)	1036 (88.4)
Subjects Discontinued	34 (12.4)	29 (10.6)	37 (13.4)	40 (14.5)	62 (10.0)	67 (10.8)	133 (11.3)	136 (11.6)
Primary Reason for Discontinuation								
- Adverse Event	14 (5.1)	4 (1.5)	16 (5.8)	10 (3.6)	25 (4.0)	12 (1.9)	55 (4.7)	26 (2.2)
- Withdrawal by Subject	13 (4.7)	22 (8.1)	13 (4.7)	18 (6.5)	20 (3.2)	25 (4.0)	46 (3.9)	65 (5.5)
- Lost to Follow-up	3 (1.1)	2 (0.7)	1 (0.4)	4 (1.4)	5 (0.8)	5 (0.8)	9 (0.8)	11 (0.9)
- Protocol Violation	1 (0.4)	1 (0.4)	5 (1.8)	7 (2.5)	5 (0.8)	13 (2.1)	11 (0.9)	21 (1.8)
- Death	0	0	1 (0.4)	0	0	3 (0.5)	1 (0.1)	3 (0.3)
- Other	3 (1.1)	0	1 (0.4)	1 (0.4)	7 (1.1)	9 (1.4)	11 (0.9)	10 (0.9)

NAL : Naldemedine, PBO : Placebo

Note: 'Overall' in this table includes one subject randomised twice in the PBO group [redacted] and counted as withdrawal by subject, one subject randomised twice in the NAL group [redacted] and counted as discontinued due to other and completed, one subjects randomised twice, once in each group [redacted] and counted as discontinued due to protocol violation and completed, one subject randomised twice, once in each group [redacted] and counted as discontinued due to protocol violation, one subject randomised twice in the PBO group [redacted] and counted as completed.

Subjects who withdrew from the study prior to Day 84 (12 weeks) were considered as Subjects Discontinued. Other subjects were considered as Subjects Completed.

Source: CTD Section 5.3.5.3, Table 14.1.2-1.1-1

Table 21 Subject Disposition in Treatment Period (Global Placebo-controlled Phase 2b and Phase 3) – All Randomised Subjects

	V9221				V9231 + V9232		V9235		Overall	
	NAL 0.1 mg N=61 n (%)	NAL 0.2 mg N=61 n (%)	NAL 0.4 mg N=61 n (%)	PBO N=61 n (%)	NAL 0.2 mg N=551 n (%)	PBO N=549 n (%)	NAL 0.2 mg N=623 n (%)	PBO N=623 n (%)	NAL 0.2 mg N=1235 n (%)	PBO N=1233 n (%)
Subjects Completed	55 (90.2)	54 (88.5)	52 (85.2)	55 (90.2)	470 (85.3)	470 (85.6)	413 (66.3)	413 (66.3)	937 (75.9)	938 (76.1)
Subjects Discontinued	6 (9.8)	7 (11.5)	9 (14.8)	6 (9.8)	81 (14.7)	79 (14.4)	210 (33.7)	210 (33.7)	298 (24.1)	295 (23.9)
Primary Reason for Discontinuation										
- Adverse Event	1 (1.6)	4 (6.6)	5 (8.2)	1 (1.6)	30 (5.4)	16 (2.9)	40 (6.4)	37 (5.9)	74 (6.0)	54 (4.4)
- Pregnancy	0	0	0	0	0	0	0	1 (0.2)	0	1 (0.1)
- Withdrawal by Subject	1 (1.6)	2 (3.3)	1 (1.6)	0	31 (5.6)	43 (7.8)	62 (10.0)	69 (11.1)	95 (7.7)	112 (9.1)
- Lost to Follow-up	0	0	1 (1.6)	0	9 (1.6)	10 (1.8)	53 (8.5)	40 (6.4)	62 (5.0)	50 (4.1)
- Protocol Violation	1 (1.6)	1 (1.6)	1 (1.6)	2 (3.3)	6 (1.1)	9 (1.6)	34 (5.5)	38 (6.1)	41 (3.3)	49 (4.0)
- Use of Prohibited Treatment	3 (4.9)	0	0	2 (3.3)	0	0	0	0	0	2 (0.2)
- Death	0	0	0	0	1 (0.2)	0	3 (0.5)	4 (0.6)	4 (0.3)	4 (0.3)
- Other	0	0	1 (1.6)	1 (1.6)	4 (0.7)	1 (0.2)	18 (2.9)	21 (3.4)	22 (1.8)	23 (1.9)

NAL : Naldemedine, PBO : Placebo

Note: 'Overall' in this table includes one subject randomised twice in the PBO group [redacted] and counted as withdrawal by subject, one subject randomised twice in the NAL group [redacted] and counted as discontinued due to other and protocol violation, two subjects randomised twice, once in each group (PBO and NAL: [redacted] and counted as discontinued due to protocol violation, one subject randomised twice in the PBO group [redacted] and counted as completed and discontinued due to protocol violation.

Source: CTD Section 5.3.5.3, Table 14.1.2-1.1-3

Cancer and OIC

Table 22 Subject Disposition in Treatment Period (Japan Cancer Phase 2 and Phase 3) – All Randomised or Enrolled Subjects

	V9222 + V9236				V9237
	Naldemedine 0.1 mg N=56 n (%)	Naldemedine 0.2 mg N=155 n (%)	Naldemedine 0.4 mg N=56 n (%)	Placebo N=153 n (%)	Naldemedine 0.2 mg N=131 n (%)
Subjects Completed	52 (92.9)	137 (88.4)	48 (85.7)	141 (92.2)	107 (81.7)
Subjects Discontinued	4 (7.1)	18 (11.6)	8 (14.3)	12 (7.8)	24 (18.3)
Primary Reason for Discontinuation					
- Adverse Event	3 (5.4)	11 (7.1)	4 (7.1)	2 (1.3)	12 (9.2)
- Withdrawal by Subject	1 (1.8)	2 (1.3)	3 (5.4)	2 (1.3)	1 (0.8)
- Ineligibility	0	0	0	2 (1.3)	0
- Poor Response or Aggravation	0	0	0	1 (0.7)	0
- Other	0	5 (3.2)	1 (1.8)	5 (3.3)	11 (8.4)

Source: CTD Section 5.3.5.3, Table 14.1.2-1.1-2

Demographics and baseline opioid consumption

Non-cancer and OIC

Table 23 Demographic and Baseline Characteristics (Global Placebo-controlled Phase 3 up to First 12 weeks) – Safety Population

	V9231		V9232		V9235		Overall		
	NAL 0.2 mg N=271	PBO N=272	NAL 0.2 mg N=271	PBO N=274	NAL 0.2 mg N=621	PBO N=619	NAL 0.2 mg N=1163	PBO N=1165	Total N=2328
Age (years)									
n	271	272	271	274	621	619	1163	1165	2328
Mean	53.3	53.4	54.2	52.9	53.4	52.7	53.6	52.9	53.2
SD	10.45	11.03	10.41	11.40	11.68	10.55	11.11	10.87	10.99
Min	19	26	25	19	20	21	19	19	19
Median	53.0	53.0	54.0	54.0	54.0	53.0	54.0	54.0	54.0
Max	79	78	79	79	80	79	80	79	80
Age Category (years), n (%)									
<40	25 (9.2)	26 (9.6)	21 (7.7)	40 (14.6)	75 (12.1)	68 (11.0)	121 (10.4)	134 (11.5)	255 (11.0)
>=40 to <65	208 (76.8)	199 (73.2)	206 (76.0)	196 (71.5)	445 (71.7)	475 (76.7)	859 (73.9)	870 (74.7)	1729 (74.3)
>=65	38 (14.0)	47 (17.3)	44 (16.2)	38 (13.9)	101 (16.3)	76 (12.3)	183 (15.7)	161 (13.8)	344 (14.8)
>=75	6 (2.2)	8 (2.9)	9 (3.3)	5 (1.8)	22 (3.5)	10 (1.6)	37 (3.2)	23 (2.0)	60 (2.6)
Gender, n (%)									
Male	110 (40.6)	104 (38.2)	110 (40.6)	106 (38.7)	238 (38.3)	217 (35.1)	458 (39.4)	427 (36.7)	885 (38.0)
Female	161 (59.4)	168 (61.8)	161 (59.4)	168 (61.3)	383 (61.7)	402 (64.9)	705 (60.6)	738 (63.3)	1443 (62.0)

NAL : Naldemedine, PBO : Placebo

Source: CTD Section 5.3.5.3, Table 14.1.2-2.1-1

Table 24 Demographic and Baseline Characteristics (Global Placebo-controlled Phase 3 up to First 12 weeks) – Safety Population (Continued)

	V9231		V9232		V9235		Overall		
	NAL 0.2 mg N=271	PBO N=272	NAL 0.2 mg N=271	PBO N=274	NAL 0.2 mg N=621	PBO N=619	NAL 0.2 mg N=1163	PBO N=1165	Total N=2328
Body Weight (kg)									
n	270	272	271	273	621	619	1162	1164	2326
Mean	89.74	90.16	89.30	89.07	90.53	90.01	90.06	89.82	89.94
SD	23.903	22.950	21.286	22.190	23.449	23.906	23.058	23.276	23.162
Min	47.7	48.0	43.6	41.0	40.4	41.0	40.4	41.0	40.4
Median	86.40	88.80	86.90	86.10	88.50	86.60	87.50	87.05	87.30
Max	188.1	169.0	173.4	163.8	200.5	197.7	200.5	197.7	200.5
BMI (kg/m^2)									
n	270	271	271	272	621	619	1162	1162	2324
Mean	31.40	31.30	31.34	31.33	31.68	31.45	31.53	31.39	31.46
SD	7.378	6.772	7.058	7.535	7.603	7.650	7.423	7.421	7.421
Min	18.7	16.7	18.4	17.9	16.0	15.1	16.0	15.1	15.1
Median	30.40	30.30	30.20	30.30	30.50	30.30	30.30	30.30	30.30
Max	57.1	63.8	59.5	58.9	68.2	68.2	68.2	68.2	68.2
BMI Category (kg/m^2), n (%)									
<18.5	0	1 (0.4)	1 (0.4)	3 (1.1)	6 (1.0)	7 (1.1)	7 (0.6)	11 (0.9)	18 (0.8)
>=18.5 to <25.0	54 (19.9)	54 (19.9)	44 (16.2)	53 (19.3)	93 (15.0)	96 (15.5)	191 (16.4)	203 (17.4)	394 (16.9)
>=25.0 to <30.0	68 (25.1)	64 (23.5)	84 (31.0)	73 (26.6)	192 (30.9)	194 (31.3)	344 (29.6)	331 (28.4)	675 (29.0)
>=30.0	148 (54.6)	152 (55.9)	142 (52.4)	143 (52.2)	330 (53.1)	322 (52.0)	620 (53.3)	617 (53.0)	1237 (53.1)
Missing	1 (0.4)	1 (0.4)	0	2 (0.7)	0	0	1 (0.1)	3 (0.3)	4 (0.2)

NAL : Naldemedine, PBO : Placebo

Source: CTD Section 5.3.5.3, Table 14.1.2-2.1-1

Table 25 Demographic and Baseline Characteristics (Global Placebo-controlled Phase 3 up to First 12 weeks) – Safety Population (Continued)

	V9231		V9232		V9235		Overall		
	NAL 0.2 mg N=271	PBO N=272	NAL 0.2 mg N=271	PBO N=274	NAL 0.2 mg N=621	PBO N=619	NAL 0.2 mg N=1163	PBO N=1165	Total N=2328
Region, n (%)									
North America	228 (84.1)	229 (84.2)	236 (87.1)	239 (87.2)	534 (86.0)	539 (87.1)	998 (85.8)	1007 (86.4)	2005 (86.1)
EU	43 (15.9)	43 (15.8)	35 (12.9)	35 (12.8)	85 (13.7)	76 (12.3)	163 (14.0)	154 (13.2)	317 (13.6)
Rest of the World	0	0	0	0	2 (0.3)	4 (0.6)	2 (0.2)	4 (0.3)	6 (0.3)
Race, n (%)									
American Indian or Alaska Native	1 (0.4)	1 (0.4)	3 (1.1)	4 (1.5)	2 (0.3)	7 (1.1)	6 (0.5)	12 (1.0)	18 (0.8)
Asian	2 (0.7)	1 (0.4)	2 (0.7)	3 (1.1)	5 (0.8)	7 (1.1)	9 (0.8)	11 (0.9)	20 (0.9)
Black or African American	53 (19.6)	48 (17.6)	48 (17.7)	39 (14.2)	120 (19.3)	108 (17.4)	221 (19.0)	195 (16.7)	416 (17.9)
Native Hawaiian or Other Pacific Islander	1 (0.4)	2 (0.7)	0	1 (0.4)	2 (0.3)	1 (0.2)	3 (0.3)	4 (0.3)	7 (0.3)
White	214 (79.0)	220 (80.9)	218 (80.4)	227 (82.8)	492 (79.2)	496 (80.1)	924 (79.4)	943 (80.9)	1867 (80.2)
Ethnicity, n (%)									
Hispanic or Latino	26 (9.6)	27 (9.9)	26 (9.6)	27 (9.9)	47 (7.6)	42 (6.8)	99 (8.5)	96 (8.2)	195 (8.4)
Not Hispanic or Latino	245 (90.4)	245 (90.1)	245 (90.4)	247 (90.1)	574 (92.4)	577 (93.2)	1064 (91.5)	1069 (91.8)	2133 (91.6)

NAL : Naldemedine, PBO : Placebo

Source: CTD Section 5.3.5.3, Table 14.1.2-2.1-1

Table 26 Average Total Daily Dose of Opioid at Baseline (Global Placebo-controlled Phase 3 up to First 12 weeks) – Safety Population

	V9231		V9232		V9235		Overall		
	NAL 0.2 mg N=271	PBO N=272	NAL 0.2 mg N=271	PBO N=274	NAL 0.2 mg N=621	PBO N=619	NAL 0.2 mg N=1163	PBO N=1165	Total N=2328
n	271	272	271	274	621	619	1163	1165	2328
Mean	125.30	139.66	117.09	123.92	123.04	121.19	122.18	126.14	124.17
SD	118.315	153.668	121.799	146.103	146.078	163.421	134.514	157.290	146.338
Min	0.0	7.5	29.0	0.0	0.0	0.0	0.0	0.0	0.0
Median	90.00	90.00	75.00	75.00	64.00	60.00	75.00	70.00	70.00
Max	730.0	1080.0	900.0	1440.0	1395.0	2560.0	1395.0	2560.0	2560.0
mg	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<30	5 (1.8)	1 (0.4)	1 (0.4)	2 (0.7)	10 (1.6)	11 (1.8)	16 (1.4)	14 (1.2)	30 (1.3)
>=30 to <=100	147 (54.2)	145 (53.3)	162 (59.8)	164 (59.9)	378 (60.9)	368 (59.5)	687 (59.1)	677 (58.1)	1364 (58.6)
>100 to <=200	67 (24.7)	72 (26.5)	70 (25.8)	63 (23.0)	131 (21.1)	149 (24.1)	268 (23.0)	284 (24.4)	552 (23.7)
>200 to <=400	43 (15.9)	39 (14.3)	27 (10.0)	34 (12.4)	77 (12.4)	62 (10.0)	147 (12.6)	135 (11.6)	282 (12.1)
>400	9 (3.3)	15 (5.5)	11 (4.1)	11 (4.0)	25 (4.0)	29 (4.7)	45 (3.9)	55 (4.7)	100 (4.3)

NAL : Naldemedine, PBO : Placebo

Dose of opioid was calculated using maintenance and breakthrough morphine equivalent dose.

Source: CTD Section 5.3.5.3, Table 14.1.2-2.2-1

In the Global Placebo-controlled Phase 3 up to First 12 Weeks safety population, demographic characteristics such as age, race, weight, average daily use of opioids, duration of opioid use, renal function and cardiovascular disease risk factors were overall similar between patients receiving naldemedine and patients receiving placebo.

Cancer and OIC

Table 27 Demographic and Baseline Characteristics (Japan Cancer Phase 2 and Phase 3) – Safety Population

	V9222 + V9236				V9237
	Naldemedine 0.1 mg N=56	Naldemedine 0.2 mg N=155	Naldemedine 0.4 mg N=56	Placebo N=152	Naldemedine 0.2 mg N=131
Age (years)					
n	56	155	56	152	131
Mean	65.9	63.7	64.2	64.4	63.5
SD	11.44	9.72	10.67	11.00	10.39
Min	41	35	41	35	35
Median	67.0	64.0	64.5	66.0	64.0
Max	83	85	86	85	85
Age Category (years), n (%)					
<40	0	4 (2.6)	0	4 (2.6)	3 (2.3)
>=40 to <65	24 (42.9)	75 (48.4)	28 (50.0)	67 (44.1)	67 (51.1)
>=65	32 (57.1)	76 (49.0)	28 (50.0)	81 (53.3)	61 (46.6)
>=75	16 (28.6)	13 (8.4)	10 (17.9)	31 (20.4)	22 (16.8)
Gender, n (%)					
Male	34 (60.7)	93 (60.0)	33 (58.9)	94 (61.8)	74 (56.5)
Female	22 (39.3)	62 (40.0)	23 (41.1)	58 (38.2)	57 (43.5)
Body Weight (kg)					
n	56	155	56	152	131
Mean	53.09	55.51	53.92	55.23	55.34
SD	9.826	9.273	9.763	11.072	11.068
Min	33.5	39.0	30.0	34.4	38.5
Median	53.30	55.00	53.50	53.65	55.00
Max	78.6	95.4	77.6	86.7	95.4
BMI (kg/m^2)					
n	56	155	56	152	131
Mean	20.60	21.63	20.93	21.08	21.42
SD	3.314	3.364	3.375	3.644	3.877
Min	15.1	15.1	13.3	14.1	14.7
Median	20.22	21.26	20.65	20.76	21.20
Max	34.6	36.6	28.3	33.5	36.6

Source: CTD Section 5.3.5.3, Table 14.1.2-2-1.2

Table 28 Demographic and Baseline Characteristics (Japan Cancer Phase 2 and Phase 3) – Safety Population (Continued)

	V9222 + V9236				V9237
	Naldemedine 0.1 mg N=56	Naldemedine 0.2 mg N=155	Naldemedine 0.4 mg N=56	Placebo N=152	Naldemedine 0.2 mg N=131
BMI Category (kg/m^2), n (%)					
<18.5	14 (25.0)	26 (16.8)	14 (25.0)	35 (23.0)	29 (22.1)
>=18.5 to <25.0	40 (71.4)	106 (68.4)	35 (62.5)	99 (65.1)	84 (64.1)
>=25.0 to <30.0	1 (1.8)	21 (13.5)	7 (12.5)	15 (9.9)	15 (11.5)
>=30.0	1 (1.8)	2 (1.3)	0	3 (2.0)	3 (2.3)
Region, n (%)					
Japan	53 (94.6)	151 (97.4)	53 (94.6)	150 (98.7)	131 (100.0)
Korea	3 (5.4)	4 (2.6)	3 (5.4)	2 (1.3)	0
Race, n (%)					
American Indian or Alaska Native	0	0	0	0	0
Asian	56 (100.0)	155 (100.0)	56 (100.0)	152 (100.0)	131 (100.0)
Black or African American	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
White	0	0	0	0	0
Ethnicity, n (%)					
Hispanic or Latino	0	0	0	0	0
Not Hispanic or Latino	56 (100.0)	155 (100.0)	56 (100.0)	152 (100.0)	131 (100.0)

Source: CTD Section 5.3.5.3, Table 14.1.2-2-1.2

Table 29 Average Total Daily Dose of Opioid at Baseline (Japan Cancer Phase 2 and Phase 3) – Safety Population

	V9222 + V9236				V9237
	Naldemedine 0.1 mg N=56	Naldemedine 0.2 mg N=155	Naldemedine 0.4 mg N=56	Placebo N=152	Naldemedine 0.2 mg N=131
n	56	155	56	152	131
Mean	77.38	66.66	54.89	75.38	63.98
SD	91.320	65.609	52.719	99.074	80.757
Min	15.0	3.0	15.0	14.8	15.0
Median	45.00	45.00	30.00	42.59	45.00
Max	480.0	360.0	270.0	720.0	720.0
mg	n (%)	n (%)	n (%)	n (%)	n (%)
<30	13 (23.2)	41 (26.5)	17 (30.4)	41 (27.0)	36 (27.5)
>=30 to <=100	33 (58.9)	87 (56.1)	30 (53.6)	81 (53.3)	76 (58.0)
>100 to <=200	6 (10.7)	18 (11.6)	8 (14.3)	17 (11.2)	14 (10.7)
>200 to <=400	3 (5.4)	9 (5.8)	1 (1.8)	11 (7.2)	4 (3.1)
>400	1 (1.8)	0	0	2 (1.3)	1 (0.8)

Dose of opioid was regular use opioid

Source: CTD Section 5.3.5.3, Table 14.1.2-2.2-2

The patients included in the cancer and OIC studies had a lower BMI and a lower baseline opioid consumption as compared to the patients included in the non-cancer and OIC studies.

Adverse events

Adverse events (AEs) reported during the study period (ie, between the first dose and the end of the follow-up period [14 or 28 days after the last dose of study drug]) are referred to as treatment-emergent adverse events (TEAEs).

Treatment-emergent adverse events have been summarised overall and by MedDRA system organ class (SOC) and preferred term (PT). When summarised by event, TEAEs that occurred more than once in the same subjects were counted only once. Summaries of TEAEs by investigator assessments of severity and of causality have also been produced. The severity of each TEAE was assessed as mild, moderate, or severe. When summarised by severity, any TEAE reported at more than one severity level, was summarised only once using the highest severity level reported. Any TEAEs that were assessed by the investigator as possibly, probably, or definitely related to the study drug were considered to be treatment-related and were summarised as ADRs. Adverse drug reactions have been summarised by SOC and PT, and by SOC, PT and severity.

An important parameter of treatment with naldemedine that requires thorough assessment is the effect of naldemedine in opioid receptors in the brain potentially leading to centrally-mediated opioid withdrawal or reversal of the analgesic effect of opioids. To assess the potential for causing centrally-mediated opioid withdrawal, AEs were grouped using two approaches:

1. The number of subjects who were reported to have had at least one TEAE or one ADR of opioid withdrawal was identified using the 'Drug withdrawal' MedDRA Standardised MedDRA Query (SMQ).

2. Subjects who had possible opioid withdrawal, defined as a subject with at least 3 TEAEs or 3 ADRs potentially related to opioid withdrawal syndrome on the same day, were identified. These events were also assessed by subgroups of events of possible opioid withdrawal with 'only nongastrointestinal PTs', 'nongastrointestinal + gastrointestinal PTs', or 'only gastrointestinal PTs'. The definition of a gastrointestinal TEAE or gastrointestinal ADR is an event belonging to the 'Gastrointestinal Disorders SOC' in MedDRA.

Overall TEAEs

Non-Cancer and OIC

Table 30 Overall Summary of Treatment-emergent Adverse Events (Global Placebo-controlled Phase 3 up to First 12 Weeks) – Safety Population

	V9231		V9232		V9235		Overall		
	NAL 0.2 mg N=271 n (%)	PBO N=272 n (%)	NAL 0.2 mg N=271 n (%)	PBO N=274 n (%)	NAL 0.2 mg N=621 n (%)	PBO N=619 n (%)	NAL 0.2 mg N=1163 n (%)	PBO N=1165 n (%)	Difference (95% CI) [a]
TEAEs	120 (44.3)	115 (42.3)	128 (47.2)	115 (42.0)	300 (48.3)	301 (48.6)	548 (47.1)	531 (45.6)	1.5 (-2.5, 5.6)
ADRs	58 (21.4)	40 (14.7)	52 (19.2)	30 (10.9)	124 (20.0)	89 (14.4)	234 (20.1)	159 (13.6)	6.5 (3.4, 9.5)
AEs Leading to Discontinuation	13 (4.8)	4 (1.5)	14 (5.2)	9 (3.3)	29 (4.7)	16 (2.6)	56 (4.8)	29 (2.5)	2.3 (0.8, 3.8)
SAEs except Deaths	11 (4.1)	5 (1.8)	8 (3.0)	9 (3.3)	27 (4.3)	24 (3.9)	46 (4.0)	38 (3.3)	0.7 (-0.8, 2.2)
SADRs	2 (0.7)	0	1 (0.4)	1 (0.4)	2 (0.3)	4 (0.6)	5 (0.4)	5 (0.4)	0.0 (-0.5, 0.5)
SAEs Leading to Discontinuation	3 (1.1)	0	3 (1.1)	3 (1.1)	3 (0.5)	3 (0.5)	9 (0.8)	6 (0.5)	0.3 (-0.4, 0.9)
Deaths	0	0	1 (0.4)	0	1 (0.2)	2 (0.3)	2 (0.2)	2 (0.2)	0.0 (-0.3, 0.3)

NAL : Naldemedine, PBO : Placebo, CI : Confidence Interval
ADRs were defined as TEAEs that were considered by the Investigator to be definitely, probably, or possibly related to IMP.
SADRs were defined as serious ADRs.
Adverse events that occurred from the first dosing date to Day 84 (12 weeks) of V9231, V9232 and V9235 were summarised.
[a] CIs based on normal approximation may not be reliable for small counts and should be interpreted with caution.
Source: CTD Section 5.3.5.3, Table 14.3-1.1-1

Table 31 Overall Summary of Treatment-emergent Adverse Events (Global Placebo-controlled Phase 2b and Phase 3) – Safety Population

	V9221				V9231 + V9232		V9235		Overall		
	NAL 0.1 mg N=61 n (%)	NAL 0.2 mg N=60 n (%)	NAL 0.4 mg N=61 n (%)	PBO N=61 n (%)	NAL 0.2 mg N=542 n (%)	PBO N=546 n (%)	NAL 0.2 mg N=621 n (%)	PBO N=619 n (%)	NAL 0.2 mg N=1223 n (%)	PBO N=1226 n (%)	Difference (95% CI) [a]
TEAEs	25 (41.0)	30 (50.0)	34 (55.7)	31 (50.8)	268 (49.4)	255 (46.7)	425 (68.4)	446 (72.1)	723 (59.1)	732 (59.7)	-0.6 (-4.5, 3.3)
ADRs	10 (16.4)	15 (25.0)	24 (39.3)	10 (16.4)	113 (20.8)	76 (13.9)	149 (24.0)	121 (19.5)	277 (22.6)	207 (16.9)	5.8 (2.6, 8.9)
AEs Leading to Discontinuation	1 (1.6)	4 (6.7)	5 (8.2)	0	27 (5.0)	13 (2.4)	39 (6.3)	36 (5.8)	70 (5.7)	49 (4.0)	1.7 (0.0, 3.4)
SAEs except Deaths	2 (3.3)	0	1 (1.6)	0	22 (4.1)	18 (3.3)	60 (9.7)	71 (11.5)	82 (6.7)	89 (7.3)	-0.6 (-2.6, 1.5)
Deaths	0	0	0	0	1 (0.2)	0	1 (0.2)	3 (0.5)	2 (0.2)	3 (0.2)	-0.1 (-0.4, 0.3)

NAL : Naldemedine, PBO : Placebo, CI : Confidence Interval
ADRs were defined as TEAEs that were considered by the Investigator to be definitely, probably, or possibly related to IMP.
[a] CIs based on normal approximation may not be reliable for small counts and should be interpreted with caution.
Source: CTD Section 5.3.5.3, Table 14.3-1.1-3

In subjects with chronic non-cancer pain and OIC, the overall incidence of TEAEs in the global placebo-controlled Phase 3 pooled population up to 12 weeks, was generally similar between groups across all 3 Phase 3 studies and in the overall pooled population. Adverse drug reactions were reported more frequently for subjects in the naldemedine group compared with subjects in the placebo group across the Phase 3 studies and in the overall pooled population. Treatment-emergent adverse events leading to discontinuation were also reported more frequently for subjects in the naldemedine group compared with subjects in the placebo group across the Phase 3 studies and in the overall pooled population.

A similar pattern was seen in the global placebo-controlled Phase 2b and Phase 3 studies pool in subjects with chronic non-cancer pain and OIC. In Study V9235, there was a higher incidence of TEAEs and SAEs

than in other studies in both treatment groups, reflecting the longer duration of this study. Overall, there was a higher incidence of ADRs in the naldemedine group compared with the placebo group with a treatment difference of 5.8% (95% CI: 2.6, 8.9). There was also a higher incidence of TEAEs leading to discontinuation (treatment difference 1.7%, 95% CI: 0.0, 3.4).

Cancer and OIC

Table 32 Overall Summary of Treatment-emergent Adverse Events (Japan Cancer Phase 2 and Phase 3) – Safety Population

	V9222 + V9236					V9237
	Naldemedine 0.1 mg N=56 n (%)	Naldemedine 0.2 mg N=155 n (%)	Naldemedine 0.4 mg N=56 n (%)	Placebo N=152 n (%)	Difference (95% CI) [a]	Naldemedine 0.2 mg N=131 n (%)
TEAEs	46 (82.1)	103 (66.5)	47 (83.9)	76 (50.0)	16.5 (5.6, 27.3)	105 (80.2)
ADRs	23 (41.1)	48 (31.0)	32 (57.1)	32 (21.1)	9.9 (0.2, 19.7)	20 (15.3)
AEs Leading to Discontinuation	3 (5.4)	11 (7.1)	4 (7.1)	2 (1.3)	5.8 (1.4, 10.2)	12 (9.2)
SAEs except Deaths	3 (5.4)	11 (7.1)	6 (10.7)	10 (6.6)	0.5 (-5.1, 6.2)	14 (10.7)
Deaths	2 (3.6)	3 (1.9)	2 (3.6)	7 (4.6)	-2.7 (-6.6, 1.3)	15 (11.5)

CI : Confidence Interval
ADRs were defined as TEAEs that were considered by the Investigator to be definitely, probably, or possibly related to IMP.
[a] Difference between Naldemedine 0.2 mg and Placebo. CIs based on normal approximation may not be reliable for small counts and should be interpreted with caution.
Source: CTD Section 5.3.5.3, Table 14.3-1.1-2

In subjects with cancer and OIC, the overall incidence of TEAEs in the Phase 2 and Phase 3 studies was generally similar between naldemedine groups (66.5% to 82.1%) in the pooled placebo-controlled Phase 2 and Phase 3 studies (V9222 and V9236) and the open-label study (V9237) but was higher than for the placebo group (50.0%) in the pooled studies. The difference between naldemedine 0.2 mg and placebo was 16.5% (95% CI: 5.6, 27.3). Adverse drug reactions were also reported more frequently for subjects in the naldemedine groups compared with subjects in the placebo group in the pooled studies, but at a lower incidence in the open-label study.

Common AEs

Non-cancer and OIC

Table 33 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term with ≥3% (Global Placebo-controlled Phase 3 up to First 12 Weeks) – Safety Population

	V9231		V9232		V9235		Overall		
System Organ Class - Preferred Term	NAL 0.2 mg N=271 n (%)	PBO N=272 n (%)	NAL 0.2 mg N=271 n (%)	PBO N=274 n (%)	NAL 0.2 mg N=621 n (%)	PBO N=619 n (%)	NAL 0.2 mg N=1163 n (%)	PBO N=1165 n (%)	Difference (95% CI) [a]
Infections and infestations									
- Urinary tract infection	6 (2.2)	5 (1.8)	6 (2.2)	11 (4.0)	9 (1.4)	23 (3.7)	21 (1.8)	39 (3.3)	-1.5 (-2.8, -0.3)
Nervous system disorders									
- Headache	6 (2.2)	3 (1.1)	6 (2.2)	3 (1.1)	14 (2.3)	19 (3.1)	26 (2.2)	25 (2.1)	0.1 (-1.1, 1.3)
Gastrointestinal disorders									
- Abdominal pain	17 (6.3)	5 (1.8)	14 (5.2)	2 (0.7)	43 (6.9)	15 (2.4)	74 (6.4)	22 (1.9)	4.5 (2.9, 6.1)
- Abdominal pain upper	5 (1.8)	2 (0.7)	4 (1.5)	2 (0.7)	22 (3.5)	13 (2.1)	31 (2.7)	17 (1.5)	1.2 (0.1, 2.4)
- Diarrhoea	18 (6.6)	6 (2.2)	23 (8.5)	5 (1.8)	49 (7.9)	17 (2.7)	90 (7.7)	28 (2.4)	5.3 (3.6, 7.1)
- Flatulence	3 (1.1)	4 (1.5)	6 (2.2)	9 (3.3)	9 (1.4)	16 (2.6)	18 (1.5)	29 (2.5)	-0.9 (-2.1, 0.2)
- Nausea	12 (4.4)	6 (2.2)	13 (4.8)	9 (3.3)	37 (6.0)	24 (3.9)	62 (5.3)	39 (3.3)	2.0 (0.3, 3.6)
- Vomiting	3 (1.1)	1 (0.4)	5 (1.8)	5 (1.8)	19 (3.1)	10 (1.6)	27 (2.3)	16 (1.4)	0.9 (-0.1, 2.0)

NAL : Naldemedine, PBO : Placebo, CI : Confidence Interval
MedDRA ver. 16.1
TEAEs with the same PT occurring more than once in a subject were counted once.
Adverse events that occurred from the first dosing date to Day 84 (12 weeks) of V9231, V9232 and V9235 were summarized.
[a] CIs based on normal approximation may not be reliable for small counts and should be interpreted with caution.
Source: CTD Section 5.3.5.3, Table 14.3-1.2.3-1

Table 34 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term with ≥5% (Global Placebo-controlled Phase 2b and Phase 3) – Safety Population

	V9221				V9231 + V9232		V9235		Overall		
System Organ Class - Preferred Term	NAL 0.1 mg N=61 n (%)	NAL 0.2 mg N=60 n (%)	NAL 0.4 mg N=61 n (%)	PBO N=61 n (%)	NAL 0.2 mg N=542 n (%)	PBO N=546 n (%)	NAL 0.2 mg N=621 n (%)	PBO N=619 n (%)	NAL 0.2 mg N=1223 n (%)	PBO N=1226 n (%)	Difference (95% CI) [a]
Infections and infestations											
- Upper respiratory tract infection	0	1 (1.7)	1 (1.6)	0	13 (2.4)	12 (2.2)	36 (5.8)	33 (5.3)	50 (4.1)	45 (3.7)	0.4 (-1.1, 1.9)
- Urinary tract infection	1 (1.6)	3 (5.0)	4 (6.6)	1 (1.6)	13 (2.4)	22 (4.0)	38 (6.1)	51 (8.2)	54 (4.4)	74 (6.0)	-1.6 (-3.4, 0.1)
Nervous system disorders											
- Headache	1 (1.6)	2 (3.3)	3 (4.9)	0	12 (2.2)	6 (1.1)	29 (4.7)	33 (5.3)	43 (3.5)	39 (3.2)	0.3 (-1.1, 1.8)
Gastrointestinal disorders											
- Abdominal pain	3 (4.9)	5 (8.3)	9 (14.8)	1 (1.6)	31 (5.7)	8 (1.5)	51 (8.2)	19 (3.1)	87 (7.1)	28 (2.3)	4.8 (3.2, 6.5)
- Abdominal pain upper	1 (1.6)	2 (3.3)	4 (6.6)	0	10 (1.8)	4 (0.7)	30 (4.8)	18 (2.9)	42 (3.4)	22 (1.8)	1.6 (0.4, 2.9)
- Diarrhoea	3 (4.9)	3 (5.0)	11 (18.0)	3 (4.9)	42 (7.7)	13 (2.4)	68 (11.0)	33 (5.3)	113 (9.2)	49 (4.0)	5.2 (3.3, 7.2)
- Flatulence	3 (4.9)	3 (5.0)	2 (3.3)	2 (3.3)	9 (1.7)	13 (2.4)	11 (1.8)	17 (2.7)	23 (1.9)	32 (2.6)	-0.7 (-1.9, 0.4)
- Nausea	1 (1.6)	4 (6.7)	3 (4.9)	1 (1.6)	26 (4.8)	16 (2.9)	49 (7.9)	35 (5.7)	79 (6.5)	52 (4.2)	2.2 (0.4, 4.0)
- Vomiting	0	0	2 (3.3)	0	8 (1.5)	7 (1.3)	37 (6.0)	19 (3.1)	45 (3.7)	26 (2.1)	1.6 (0.2, 2.9)
Musculoskeletal and connective tissue disorders											
- Arthralgia	1 (1.6)	1 (1.7)	1 (1.6)	4 (6.6)	9 (1.7)	6 (1.1)	29 (4.7)	23 (3.7)	39 (3.2)	33 (2.7)	0.5 (-0.8, 1.8)
- Back pain	1 (1.6)	0	1 (1.6)	4 (6.6)	16 (3.0)	15 (2.7)	36 (5.8)	31 (5.0)	52 (4.3)	50 (4.1)	0.2 (-1.4, 1.8)

NAL : Naldemedine, PBO : Placebo, CI : Confidence Interval

MedDRA ver. 16.1

TEAEs with the same PT occurring more than once in a subject were counted once.

[a] CIs based on normal approximation may not be reliable for small counts and should be interpreted with caution.

Source: CTD Section 5.3.5.3, Table 14.3-1.2.4-3

In the naldemedine global placebo-controlled Phase 3 pooled population up to 12 weeks, the overall incidence of TEAEs was generally similar between groups across all 3 Phase 3 studies separately and in the overall pooled population. Incidences of TEAEs by SOC were also generally similar between groups across all 3 Phase 3 studies separately and in the overall pooled population, except for the Gastrointestinal Disorders SOC, in which the incidence of TEAEs was higher in the naldemedine treatment group (21.8%) compared with the placebo treatment group (13.9%) in the overall pooled population, with a difference between groups of 7.8% (95% CI: 4.8, 10.9). The incidence of TEAEs in the Gastrointestinal Disorders SOC was also higher in the naldemedine group than the placebo group in each of the individual studies.

The overall incidence of TEAEs in the global placebo-controlled Phase 2b and Phase 3 population was generally similar between groups across all 4 studies separately and in the overall pooled population as seen in the global placebo-controlled Phase 3 population up to 12 weeks. The incidence of TEAEs was higher in the long-term Study V9235 than in other studies (Table 2.7.4 - 19). Incidences of TEAEs by SOC were also generally similar between groups across all studies separately and in the overall pooled population, except for the Gastrointestinal Disorders SOC, in which the incidence of TEAEs was higher in the naldemedine treatment group (27.3%) compared with the placebo treatment group (19.7%) in the overall pooled population, with a difference between groups of 7.7% (95% CI: 4.3, 11.0). The treatment difference was similar to that seen in the global Phase 3 population up to 12 weeks (7.8%; 95% CI: 4.8, 10.9). In the long-term study the incidence of TEAEs in the Gastrointestinal Disorders SOC was 32.7% for naldemedine 0.2 mg and 25.5% for placebo.

Cancer and OIC

Table 35 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term with ≥5% (Japan Cancer Phase 2 and Phase 3) – Safety Population

	V9222 + V9236					V9237
System Organ Class - Preferred Term	Naldemedine 0.1 mg N=56 n (%)	Naldemedine 0.2 mg N=155 n (%)	Naldemedine 0.4 mg N=56 n (%)	Placebo N=152 n (%)	Difference (95% CI) [a]	Naldemedine 0.2 mg N=131 n (%)
Infections and infestations						
- Nasopharyngitis	0	4 (2.6)	2 (3.6)	4 (2.6)	-0.1 (-3.6, 3.5)	9 (6.9)
Blood and lymphatic system disorders						
- Anaemia	2 (3.6)	4 (2.6)	2 (3.6)	5 (3.3)	-0.7 (-4.5, 3.1)	8 (6.1)
- Bone marrow failure	0	2 (1.3)	3 (5.4)	3 (2.0)	-0.7 (-3.5, 2.2)	1 (0.8)
Metabolism and nutrition disorders						
- Decreased appetite	3 (5.4)	9 (5.8)	6 (10.7)	2 (1.3)	4.5 (0.4, 8.6)	14 (10.7)
Psychiatric disorders						
- Insomnia	1 (1.8)	1 (0.6)	0	2 (1.3)	-0.7 (-2.9, 1.5)	7 (5.3)
Gastrointestinal disorders						
- Abdominal pain	2 (3.6)	5 (3.2)	3 (5.4)	1 (0.7)	2.6 (-0.5, 5.6)	3 (2.3)
- Diarrhoea	16 (28.6)	45 (29.0)	32 (57.1)	24 (15.8)	13.2 (4.0, 22.4)	24 (18.3)
- Nausea	5 (8.9)	7 (4.5)	3 (5.4)	9 (5.9)	-1.4 (-6.4, 3.6)	17 (13.0)
- Vomiting	5 (8.9)	6 (3.9)	3 (5.4)	2 (1.3)	2.6 (-1.0, 6.1)	16 (12.2)

CI : Confidence Interval
MedDRA ver. 16.1
TEAEs with the same PT occurring more than once in a subject were counted once.
[a] Difference between Naldemedine 0.2 mg and Placebo. CIs based on normal approximation may not be reliable for small counts and should be interpreted with caution.
Source: CTD Section 5.3.5.3, Table 14.3-1.2.3-2

Table 36 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term with ≥5% (Japan Cancer Phase 2 and Phase 3) – Safety Population

Table 2.7.4 - 23 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term with ≥ 5% (Japan Cancer Phase 2 and Phase 3) - Safety Population (Continued)

	V9222 + V9236					V9237
System Organ Class - Preferred Term	Naldemedine 0.1 mg N=56 n (%)	Naldemedine 0.2 mg N=155 n (%)	Naldemedine 0.4 mg N=56 n (%)	Placebo N=152 n (%)	Difference (95% CI) [a]	Naldemedine 0.2 mg N=131 n (%)
General disorders and administration site conditions						
- Malaise	1 (1.8)	7 (4.5)	0	2 (1.3)	3.2 (-0.5, 6.9)	13 (9.9)
Investigations						
- Blood pressure increased	3 (5.4)	0	1 (1.8)	0	0.0 (---, ---)	0
- Protein total decreased	3 (5.4)	7 (4.5)	2 (3.6)	2 (1.3)	3.2 (-0.5, 6.9)	0
- Protein urine present	8 (14.3)	4 (2.6)	0	2 (1.3)	1.3 (-1.8, 4.3)	0
- Red blood cell count decreased	3 (5.4)	2 (1.3)	0	0	1.3 (-0.5, 3.1)	0
- White blood cell count decreased	2 (3.6)	10 (6.5)	5 (8.9)	8 (5.3)	1.2 (-4.1, 6.4)	2 (1.5)

CI : Confidence Interval
MedDRA ver. 16.1
TEAEs with the same PT occurring more than once in a subject were counted once.
[a] Difference between Naldemedine 0.2 mg and Placebo. CIs based on normal approximation may not be reliable for small counts and should be interpreted with caution.
Source: CTD Section 5.3.5.3, Table 14.3-1.2.3-2

In subjects with cancer and OIC, the overall iidence of TEAEs in the Phase 2 and Phase 3 studies was generally similar between naldemedine groups in the pooled placebo-controlled Phase 2 and Phase 3 studies (V9222 and V9236) and the open-label study (V9237) but was higher than for the placebo group in the pooled placebo-controlled studies. In the pooled population of Studies V9222 and V9236, incidences of TEAEs by SOC were generally similar between the naldemedine 0.2 mg group and the placebo group except for the Metabolism and Nutrition Disorders SOC in which the incidence of TEAEs was higher in the naldemedine 0.2 mg treatment group (8.4%) compared with the placebo treatment group (2.6%) with a difference between groups of 5.8% (95% CI: 0.7; 10.8) and the Gastrointestinal Disorders SOC in which the incidence of TEAEs in the naldemedine treatment group (36.8%) was also higher

compared with the placebo treatment group (23.0%) with a difference between groups of 13.7% (95% CI: 3.6; 23.9). The difference between groups in the Metabolism and Nutrition Disorders SOC was driven by a higher incidence of TEAEs of decreased appetite in the naldemedine groups compared with the placebo group. The difference observed between groups in the Gastrointestinal Disorders SOC was mainly driven by a higher incidence of TEAEs of diarrhoea in the naldemedine groups compared with the placebo group.

AEs by severity

Non-cancer and OIC

In the global, placebo-controlled Phase 3 studies up to 12 weeks, severe TEAEs were reported for 63 (5.4%) subjects in the naldemedine group and 45 (3.9%) subjects in the placebo group. The specific TEAEs most commonly reported as severe were abdominal pain (11 [0.9%] subjects in the naldemedine group and 3 [0.3%] subjects in the placebo group) and diarrhoea (7 [0.6%] subjects in the naldemedine group and 4 [0.3%] subjects in the placebo group). The only other specific TEAEs reported as severe for more than 2 subjects in the overall naldemedine group were headache (4 [0.3%] subjects for naldemedine and 3 [0.3%] subjects for placebo), abdominal pain upper (3 [0.3% subjects for naldemedine and 1 [0.1%] subjects for placebo), arthralgia (3 [0.3%] subjects for naldemedine and none for placebo), and back pain (4 [0.3%] subjects for naldemedine and 3 [0.3%] subjects for placebo). With the exception of gastrointestinal TEAEs of abdominal pain and diarrhoea, there was no evidence observed for increased severity of TEAEs with naldemedine treatment.

Overall, there were 23 (2.0%) subjects in the naldemedine group and 15 (1.3%) subjects in the placebo group with ADRs that were considered to be severe. The only specific ADRs reported as severe in more than 1 subject in the naldemedine group were gastrointestinal ADRs: abdominal pain, abdominal pain upper, diarrhoea, and abdominal distension.

Similar results for severity of TEAEs and ADRs were seen for the global, placebo-controlled Phase 2b and Phase 3 studies (including long-term Study V9235) and there was no evidence observed that the severity of TEAEs or ADRs increased with long-term treatment. In the overall pooled population, severe TEAEs were reported for 101 (8.3%) subjects in the naldemedine group and 89 (7.3%) subjects in the placebo group and severe ADRs were reported for 27 (2.2%) subjects in the naldemedine group and 17 (1.4%) subjects in the placebo group. The only ADRs reported as severe for more than 1 subject in the pooled naldemedine group were gastrointestinal ADRs (abdominal distension, abdominal pain, abdominal pain upper, and diarrhoea) and pulmonary embolism (2 [0.2%] subjects in the naldemedine group and no subjects in the placebo group). The severe pulmonary embolism ADRs were both SAEs reported in Study V9235. One subject who had an SAE of adenocarcinoma which subsequently led to the subject's death experienced a deep vein thrombosis of moderate intensity and a myocardial infarction of severe intensity in addition to the pulmonary embolism. Another subject experienced SAEs of pneumonia and pulmonary embolism.

Cancer and OIC

In the V9222 and V9236 pooled population, severe TEAEs were reported for 9 (16.1%) subjects in the naldemedine 0.1 mg group, 28 (18.1%) subjects in the naldemedine 0.2 mg group, 10 (17.9%) subjects in the naldemedine 0.4 mg group and 25 (16.4%) subjects in the placebo group. In the open-label Study V9237, severe TEAEs were reported for 40 (30.5%) subjects treated with naldemedine. The most commonly reported severe TEAEs were consistent with the subject's underlying medical history of cancer. For the pooled population, the specific TEAEs reported as severe in more than 2 subjects in the naldemedine 0.2 mg group were anaemia (4 [2.6%] in the naldemedine 0.2 mg group and 3 [2.0%] in the placebo group) and white blood cell count decreased (3 [1.9%] in the naldemedine 0.2 mg group and

2 [1.3%] in the placebo group). In the open-label Study V9237, TEAEs in the Neoplasms Benign, Malignant, and Unspecified SOC were reported as severe for 16 (12.2%) subjects. Other TEAEs reported as severe in this study in more than 2 (1.5%) subjects were anaemia (5.3%), decreased appetite (3.1%), febrile neutropenia (2.3%), and thrombocytopenia (2.3%). Few ADRs were reported as severe. In the V9222 and V9236 pooled population, severe ADRs were reported for 2 (3.6%) subjects in the naldemedine 0.1 mg group, 2 (1.3%) subjects in the naldemedine 0.2 mg group, 2 (3.6%) subjects in the naldemedine 0.4 mg group and 2 (1.3%) subjects in the placebo group. In the open-label Study V9237, severe TEAEs were reported for 1 (0.8%) subject treated with naldemedine.

Liver events and MACE

Overall, no safety signals with regard to liver events or MACE were detected for any of the study populations.

Opioid withdrawal

Non-cancer and OIC

Table 37 Proportion of Subjects with an Adverse Drug Reaction of Opioid Withdrawal or with Possible Opioid Withdrawal While on Treatment (Global Placebo-controlled Phase 3 up to First 12 Weeks) – Safety Population

	V9231		V9232		V9235		Overall	
	NAL 0.2 mg N=271 n (%)	PBO N=272 n (%)	NAL 0.2 mg N=271 n (%)	PBO N=274 n (%)	NAL 0.2 mg N=621 n (%)	PBO N=619 n (%)	NAL 0.2 mg N=1163 n (%)	PBO N=1165 n (%)
Subjects with an ADR of OW [a]	2 (0.7)	1 (0.4)	0	0	8 (1.3)	5 (0.8)	10 (0.9)	6 (0.5)
Subjects with Possible OW [b]	1 (0.4)	1 (0.4)	4 (1.5)	1 (0.4)	9 (1.4)	1 (0.2)	14 (1.2)	3 (0.3)
- Subjects with Possible OW only non-GI PTs [c]	0	0	0	0	0	0	0	0
- Subjects with Possible OW non-GI + GI PTs [d]	0	0	3 (1.1)	1 (0.4)	6 (1.0)	1 (0.2)	9 (0.8)	2 (0.2)
- Subjects with Possible OW only GI PTs [e]	1 (0.4)	1 (0.4)	1 (0.4)	0	3 (0.5)	0	5 (0.4)	1 (0.1)

NAL : Naldemedine, PBO : Placebo

[a] OW: opioid withdrawal based on SMQ (Drug withdrawal).

[b] Possible OW based on OW terms of those subjects with at least 3 ADR of PTs potentially related to opioid withdrawal syndrome which has onset on the same day or occurred within one day.

[c] All non-GI ADR of PTs with at least 3 ADR of PTs potentially related to opioid withdrawal syndrome. GI includes 'Gastrointestinal disorders' in MedDRA SOC.

[d] At least one GI ADR of PT and at least one non-GI ADR of PT out of at least 3 ADR of PTs potentially related to opioid withdrawal syndrome.

[e] All GI ADR of PTs with at least 3 ADR of PTs potentially related to opioid withdrawal syndrome.

ADRs which occurred after last dose day + 5 days were excluded

Source: CTD Section 5.3.5.3, Table 14.3-2.6-1

In the global Phase 3 pooled population up to 12 weeks, the incidence of ADRs of opioid withdrawal was generally low across the 3 studies and the overall pooled population. No events were reported in Study V9232, while in studies V9231 and V9235, ADRs of opioid withdrawal were reported at a numerically higher incidence in the naldemedine group compared with the placebo group. Similarly, in the overall pooled population, ADRs of opioid withdrawal were reported with a numerically higher frequency (0.9%) in the naldemedine group compared with the placebo group (0.5%).

Cancer and OIC

Table 38 Proportion of Subjects with an Adverse Drug Reaction of Opioid Withdrawal or with possible Opioid Withdrawal while on Treatment (Japan Cancer Phase 2 and Phase 3) – Safety Population

	V9222 + V9236				V9237
	Naldemedine 0.1 mg N=56 n (%)	Naldemedine 0.2 mg N=155 n (%)	Naldemedine 0.4 mg N=56 n (%)	Placebo N=152 n (%)	Naldemedine 0.2 mg N=131 n (%)
Subjects with an ADR of OW [a]	0	0	0	0	0
Subjects with Possible OW [b]	0	1 (0.6)	2 (3.6)	0	1 (0.8)
- Subjects with Possible OW only non-GI PTs [c]	0	0	1 (1.8)	0	1 (0.8)
- Subjects with Possible OW non-GI + GI PTs [d]	0	1 (0.6)	0	0	0
- Subjects with Possible OW only GI PTs [e]	0	0	1 (1.8)	0	0

[a] OW: opioid withdrawal based on SMQ (Drug withdrawal).

[b] Possible OW based on OW terms of those subjects with at least 3 ADR of PTs potentially related to opioid withdrawal syndrome which has onset on the same day or occurred within one day.

[c] All non-GI ADR of PTs with at least 3 ADR of PTs potentially related to opioid withdrawal syndrome. GI includes 'Gastrointestinal disorders' in MedDRA SOC.

[d] At least one GI ADR of PT and at least one non-GI ADR of PT out of at least 3 ADR of PTs potentially related to opioid withdrawal syndrome.

[e] All GI ADR of PTs with at least 3 ADR of PTs potentially related to opioid withdrawal syndrome.

ADRs which occurred after last dose day + 5 days were excluded

Source: CTD Section 5.3.5.3, Table 14.3-2.6-2

In the Phase 2 and Phase 3 studies in subjects with cancer and OIC, no ADRs of opioid withdrawal were reported. The incidence of ADRs of possible opioid withdrawal was low, however, all ADRs were identified for subjects in the naldemedine groups and no events were identified for subjects in the placebo group. For subjects in the naldemedine 0.2 mg group in Studies V9222 and V9236, only 1 event composed of gastrointestinal and nongastrointestinal PTs was identified. In Study V9237, only 1 event composed of nongastrointestinal PTs was identified.

Gastrointestinal perforation

There were no events of gastrointestinal perforation reported in the naldemedine clinical program.

Serious adverse event / deaths / other significant events

SAEs

Non-Cancer and OIC

Assessment of the incidence of non-fatal SAEs in the global Phase 3 pooled population up to 12 weeks, did not lead to identification of specific safety trends of concern. The overall incidence of SAEs was low and similar in both treatment groups.

Table 39 Incidence of SAEs except Deaths by System Organ Class and Preferred Term (Global Ph3 up to First 12 Weeks) Safety Population

System Organ Class - Preferred Term	V9231 NAL 0.2 mg N=271 n (%)	V9231 PBO N=272 n (%)	V9232 NAL 0.2 mg N=271 n (%)	V9232 PBO N=274 n (%)	V9235 NAL 0.2 mg N=621 n (%)	V9235 PBO N=619 n (%)	Overall NAL 0.2 mg N=1163 n (%)	Overall PBO N=1165 n (%)	Difference (95% CI) [a]
Subjects with SAEs except Deaths	11 (4.1)	5 (1.8)	8 (3.0)	9 (3.3)	27 (4.3)	24 (3.9)	46 (4.0)	38 (3.3)	0.7 (-0.8, 2.2)
Infections and infestations	1 (0.4)	1 (0.4)	2 (0.7)	2 (0.7)	8 (1.3)	8 (1.3)	11 (0.9)	11 (0.9)	0.0 (-0.8, 0.8)
- Appendicitis	1 (0.4)	0	0	0	0	0	1 (0.1)	0	0.1 (-0.1, 0.3)
- Arthritis bacterial	0	0	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.1, 0.3)
- Cellulitis	0	0	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.1, 0.3)
- Herpes zoster	0	0	1 (0.4)	0	0	0	1 (0.1)	0	0.1 (-0.1, 0.3)
- Incision site infection	0	0	0	0	0	1 (0.2)	0	1 (0.1)	-0.1 (-0.3, 0.1)
- Infected skin ulcer	0	0	0	0	0	1 (0.2)	0	1 (0.1)	-0.1 (-0.3, 0.1)
- Lobar pneumonia	0	0	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)	0.0 (-0.2, 0.2)
- Localised infection	0	0	0	0	0	1 (0.2)	0	1 (0.1)	-0.1 (-0.3, 0.1)
- Otitis media	0	0	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.1, 0.3)
- Parotitis	0	0	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.1, 0.3)
- Pneumonia	0	1 (0.4)	0	1 (0.4)	3 (0.5)	2 (0.3)	3 (0.3)	4 (0.3)	-0.1 (-0.5, 0.4)

NAL : Naldemedine, PBO : Placebo, CI : Confidence Interval
MedDRA ver. 16.1
SAEs except deaths with the same PT occurring more than once in a subject were counted once.
Adverse events that occurred from the first dosing date to Day 84 (12 weeks) of V9231, V9232 and V9235 were summarized.
[a] CIs based on normal approximation may not be reliable for small counts and should be interpreted with caution.
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Table 40 Incidence of SAEs except Deaths by System Organ Class and Preferred Term (Global Ph2 and 3) Safety Population

System Organ Class - Preferred Term	V9221 NAL 0.1 mg N=61 n (%)	V9221 NAL 0.2 mg N=60 n (%)	V9221 NAL 0.4 mg N=61 n (%)	V9221 PBO N=61 n (%)	V9231 + V9232 NAL 0.2 mg N=542 n (%)	V9231 + V9232 PBO N=546 n (%)	V9235 NAL 0.2 mg N=621 n (%)	V9235 PBO N=619 n (%)	Overall NAL 0.2 mg N=1223 n (%)	Overall PBO N=1226 n (%)	Difference (95% CI) [a]
Subjects with SAEs except Deaths	2 (3.3)	0	1 (1.6)	0	22 (4.1)	18 (3.3)	60 (9.7)	71 (11.5)	82 (6.7)	89 (7.3)	-0.6 (-2.6, 1.5)
Infections and infestations	1 (1.6)	0	0	0	3 (0.6)	4 (0.7)	15 (2.4)	19 (3.1)	18 (1.5)	23 (1.9)	-0.4 (-1.4, 0.6)
- Appendicitis	1 (1.6)	0	0	0	1 (0.2)	0	1 (0.2)	0	2 (0.2)	0	0.2 (-0.1, 0.4)
- Arthritis bacterial	0	0	0	0	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.1, 0.2)
- Bronchitis	0	0	0	0	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.1, 0.2)
- Cellulitis	0	0	0	0	0	0	2 (0.3)	2 (0.3)	2 (0.2)	2 (0.2)	0.0 (-0.3, 0.3)
- Cellulitis orbital	0	0	0	0	0	0	0	1 (0.2)	0	1 (0.1)	-0.1 (-0.2, 0.1)
- Gastroenteritis viral	0	0	0	0	0	1 (0.2)	0	0	0	1 (0.1)	-0.1 (-0.2, 0.1)
- Herpes zoster	0	0	0	0	1 (0.2)	0	0	0	1 (0.1)	0	0.1 (-0.1, 0.2)
- Incision site infection	0	0	0	0	0	0	0	1 (0.2)	0	1 (0.1)	-0.1 (-0.2, 0.1)
- Infected skin ulcer	0	0	0	0	0	0	0	1 (0.2)	0	1 (0.1)	-0.1 (-0.2, 0.1)
- Lobar pneumonia	0	0	0	0	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)	0.0 (-0.2, 0.2)
- Localised infection	0	0	0	0	0	0	0	1 (0.2)	0	1 (0.1)	-0.1 (-0.2, 0.1)
- Necrotising fasciitis	0	0	0	0	0	0	0	1 (0.2)	0	1 (0.1)	-0.1 (-0.2, 0.1)

NAL : Naldemedine, PBO : Placebo, CI : Confidence Interval
MedDRA ver. 16.1
SAEs except deaths with the same PT occurring more than once in a subject were counted once.
[a] CIs based on normal approximation may not be reliable for small counts and should be interpreted with caution.
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Cancer and OIC

Assessment of the incidence of non-fatal SAEs in the Japanese Phase 2 and Phase 3 population for subjects with cancer and OIC did not lead to identification of specific safety trends of concern. In the Phase 2 and Phase 3 pooled population, 3 (5.4%) subjects treated with naldemedine 0.1 mg, 11 (7.1%) subjects treated with naldemedine 0.2 mg, 6 (10.7%) subjects treated with naldemedine 0.4 mg, and 10

(6.6%) subjects treated with placebo were reported to have had a non-fatal SAE. In the open-label Study V9237, non-fatal SAEs were reported for 14 (10.7%) subjects.

Table 41 Incidence of SAEs except Deaths by System Organ Class and Preferred Term (Japan Cancer Ph2 and 3) Safety Population

	V9222 + V9236					V9237
System Organ Class - Preferred Term	Naldemedine 0.1 mg N=56 n (%)	Naldemedine 0.2 mg N=155 n (%)	Naldemedine 0.4 mg N=56 n (%)	Placebo N=152 n (%)	Difference (95% CI) [a]	Naldemedine 0.2 mg N=131 n (%)
Subjects with SAEs except Deaths	3 (5.4)	11 (7.1)	6 (10.7)	10 (6.6)	0.5 (-5.1, 6.2)	14 (10.7)
Infections and infestations	0	2 (1.3)	1 (1.8)	5 (3.3)	-2.0 (-5.3, 1.3)	7 (5.3)
- Gastroenteritis	0	0	0	0	0.0 (---, ---)	1 (0.8)
- Gastroenteritis norovirus	0	1 (0.6)	0	0	0.6 (-0.6, 1.9)	0
- Infection	0	0	0	1 (0.7)	-0.7 (-1.9, 0.6)	1 (0.8)
- Pneumonia	0	1 (0.6)	1 (1.8)	3 (2.0)	-1.3 (-3.9, 1.2)	2 (1.5)
- Pneumonia bacterial	0	0	0	0	0.0 (---, ---)	1 (0.8)
- Pneumonia pneumococcal	0	0	0	1 (0.7)	-0.7 (-1.9, 0.6)	1 (0.8)
- Sepsis	0	0	0	1 (0.7)	-0.7 (-1.9, 0.6)	0
- Urinary tract infection	0	0	0	0	0.0 (---, ---)	1 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	0.0 (---, ---)	1 (0.8)
- Chronic myelomonocytic leukaemia	0	0	0	0	0.0 (---, ---)	1 (0.8)

Deaths

During the naldemedine clinical programme there were 39 subjects who died. None were considered by the investigators to be related to study treatment. In subjects with chronic non-cancer pain and OIC, in placebo-controlled studies there were 9 subjects who died (5 treated with naldemedine and 4 treated with placebo), and in uncontrolled, open-label, naldemedine studies 1 subject died. In subjects with cancer and OIC, in placebo-controlled studies 14 subjects died (7 treated with naldemedine and 7 treated with placebo) and in the uncontrolled, open-label study 15 subjects died.

Non-cancer and OIC – placebo-controlled

Table 42 Subjects Who Died in Placebo-controlled Phase 2 and Phase 3 Studies in Chronic Non-cancer Pain and Opioid induced Constipation

Study Group	Race / Patient ID	Sex /Age (years)	Preferred Term (Reported Term)	Timing of Onset [a] / Duration [b]	Severity / Seriousness/ Causality	Action Taken [c] Other Action Taken [d] Outcome
Phase 3 Study V9232						
Naldemedine 0.2 mg	[redacted]	Female 37	Overdose (opioid drug overdose)	9 1	Severe Serious Not related	Dose Not Changed No Fatal
Phase 3 Long-term Study V9235						
Naldemedine 0.2 mg	[redacted]	Female 52	Adenocarcinoma (stage IV adeno carcinoma)	76 94	Severe Serious Not related	Fatal
Naldemedine 0.2 mg	[redacted]	Female 58	Chronic obstructive pulmonary disease (acute exacerbation of chronic obstructive pulmonary disease)	After the follow-up period 155 8	Severe/ Serious/ Not related	Fatal
Naldemedine 0.2 mg	[redacted]	Male 49	Myocardial infarction (myocardial infarction)	After the follow-up period 346 1	Severe Serious Not related	Fatal
Naldemedine 0.2 mg	[redacted]	Female 53	Cerebrovascular accident (suspected cerebrovascular accident)	After the follow-up period 350 1	Severe Serious Not related	Fatal
Placebo	[redacted]	Male 64	Cardiac arrest (cardiac arrest)	28 1	Severe Serious Not related	Fatal
Placebo	[redacted]	Female 49	Arteriosclerosis (complications of arteriosclerotic CV disease)	31 1	Severe Serious Not related	Fatal

Table 43 Subjects Who Died in Placebo-controlled Phase 2 and Phase 3 Studies in Chronic Non-cancer Pain and Opioid induced Constipation

Study Group	Race / Patient ID	Sex /Age (years)	Preferred Term (Reported Term)	Timing of Onset [a] / Duration [b]	Severity / Seriousness/ Causality	Action Taken [c] Other Action Taken [d] Outcome
Placebo	White [redacted]	Female 78	Cerebrovascular accident (massive stroke)	175 5	Severe Serious Not related	Fatal
Placebo	Black or African American [redacted]	Male 52	Accidental overdose (accidental overdose)	After the follow-up period 50 Unknown	Severe/ Serious/ Not related	Fatal

This listing includes all TEAEs in subjects with deaths.

a Relative Day of Onset = (AE start date) - (Date of initial dose of study drug) + 1[days].

b Duration = (AE end date) - (AE start date) + 1[days].

c Action Taken = Action taken with study drug.

d Other Action Taken = Action taken with other than study drug.

MedDRA ver. 16.0

Source: V9232, Section 14.3.31 and Study V9235, Section 14.3.3.1

Table 44 Subjects Who Died in Open-label, Single-arm, Phase 3 Studies in Chronic Non-cancer Pain and Opioid-induced Constipation

Study Group	Region / Patient ID	Sex / Age (years) / Duration of Exposure (days)	Preferred Term (Reported Term)	Timing of Onset [a] / Duration [b]	Severity / Seriousness/ Causality	Action Taken [c] / Other Action Taken [d] / Outcome
Japanese Phase 3 open-label Study V9238						
Naldemedine 0.2 mg	Japan [redacted]	Male 50 308	Death (Fatal, death)	309 1 +	Severe Serious Not related	Drug withdrawn No Fatal

a Timing of Onset = (Date of onset) - (Date of initial dose of naldemedine) +1.

b Duration = (Date of outcome) - (Date of onset) +1. Plus sign shows that the adverse event did not recover and was not recovering until the day of outcome assessment.

c Action Taken = Action taken with the study drug.

d Other Action Taken = Action taken with drugs other than the study drug.

MedDRA Version: 16.1.

Source: Study V9238, Section 14.2.1

In the global placebo-controlled Phase 3 studies in subjects with chronic non-cancer pain and OIC, 5 (0.4%) subjects in the naldemedine group and 4 (0.3%) subjects in the placebo group died. One of these subjects (Subject 52415-004) was discontinued due to a TEAE but subsequently died so was not counted as a death in the disposition table. All TEAEs leading to death were considered not related to the study drug by the investigators.

In the Japanese open-label, uncontrolled studies of naldemedine (Studies V9238 and V9239), 1 subject died. This death was not considered to be related to the study drug by the investigator.

Cancer and OIC

Table 45 Subjects Who Died in Phase 2 and Phase 3 Studies in Subjects with Cancer and Opioid-induced Constipation

Study Group	Region / Patient ID	Sex / Age (years) / Duration of Exposure (days)	Preferred Term (Reported Term)	Timing of Onset [a] / Duration [b]	Severity / Seriousness / Causality	Action Taken [c] Other Action Taken [d] Outcome
Japanese Phase 2b Dose Finding Study in Cancer Patients (V9222)						
Naldemedine 0.1 mg	Japan [redacted]	Male 79 14	Metastatic small cell lung cancer (lung cancer aggravated)	29 1 +	Severe Serious Not related	Not applicable No Fatal
Naldemedine 0.1 mg	Japan [redacted]	Male 66 14	Lung neoplasm malignant (lung cancer aggravated)	29 1 +	Severe Serious Not related	Not applicable No Fatal
Naldemedine 0.4 mg	Japan [redacted]	Male 46 13	Bile duct cancer (progression of cholangiocarcinoma)	14 1 +	Severe Serious Not related	Drug withdrawn Yes Fatal
Naldemedine 0.4 mg	Japan [redacted]	Male 61 10	Lung neoplasm malignant (Lung cancer progression)	21 1 +	Severe Serious Not related	Not applicable No Fatal
Placebo	Japan [redacted]	Female 70 5	Lung neoplasm malignant (lung cancer aggravated)	10 1 +	Severe Serious Not related	Not applicable No Fatal
Placebo	Japan [redacted]	Female 50 14	Breast cancer (aggravation of primary disease)	25 1 +	Severe Serious Not related	Not applicable Yes Fatal
Placebo	Japan [redacted]	Female 61 14	Breast cancer (worsening of primary disease)	32 1 +	Severe Serious Not related	Not applicable Yes Fatal
Japanese Phase 3 Confirmation Study in Cancer Patients (V9236)						
Naldemedine 0.2 mg	Japan [redacted]	Male 73 5	Lung neoplasm malignant (aggravation of lung cancer)	10 1 +	Severe Serious Not related	Not applicable No Fatal

Table 46 Subjects Who Died in Phase 2 and Phase 3 Studies in Subjects with Cancer and Opioid-induced Constipation (Continued)

Study Group	Region / Patient ID	Sex / Age (years) / Duration of Exposure (days)	Preferred Term (Reported Term)	Timing of Onset [a] / Duration [b]	Severity / Seriousness/ Causality	Action Taken [c] Other Action Taken [d] Outcome
Naldemedine 0.2 mg	Japan [redacted]	Male 55 7	Pneumonia influenzal (influenza [pneumonia])	7 5 +	Severe Serious Not related	Drug withdrawn Yes Fatal
			Pneumonia bacterial (bacterial pneumonia)	7 5 +	Severe Serious Not related	Drug withdrawn Yes Fatal
Naldemedine 0.2 mg	Japan [redacted]	Male 69 11	Interstitial lung disease (Acute exacerbation of interstitial pneumonia)	7 7 +	Severe Serious Not related	Drug withdrawn Yes Fatal
Placebo	Japan [redacted]	Male 72 6	Lung neoplasm malignant (Aggravation of the lung cancer)	20 1 +	Severe Serious Not related	Not applicable No Fatal
Placebo	Japan [redacted]	Male 78 11	Lung neoplasm malignant (aggravation of lung cancer)	21 1 +	Severe Serious Not related	Not applicable No Fatal
Placebo	Japan [redacted]	Male 67 8	Lung neoplasm malignant (Primary disease (lung cancer) aggravated)	10 1 +	Severe Serious Not related	Not applicable No Fatal
Placebo	Japan [redacted]	Female 49 14	Phyllodes tumour (Primary disease (breast cancer) aggravation)	31 1 +	Severe Serious Not related	Not applicable No Fatal
Japanese Phase 3 Extension Study in Cancer Patients (V9237)						
Naldemedine 0.2 mg	Japan [redacted]	Male 75 84	Prostate cancer (prostate cancer aggravated)	113 1 +	Severe Serious Not related	Not applicable No Fatal
Naldemedine 0.2 mg	Japan [redacted]	Male 70 72	Lung neoplasm malignant (Aggravation of the lung cancer)	76 1 +	Severe Serious Not related	Drug withdrawn No Fatal
Naldemedine 0.2 mg	Japan [redacted]	Female 56 68	Breast cancer (aggravated of breast cancer)	69 1 +	Severe Serious Not related	Drug withdrawn No Fatal

Table 47 Subjects Who Died in Phase 2 and Phase 3 Studies in Subjects with Cancer and Opioid-induced Constipation (Continued)

Study Group	Region / Patient ID	Sex / Age (years) / Duration of Exposure (days)	Preferred Term (Reported Term)	Timing of Onset [a] / Duration [b]	Severity / Seriousness/ Causality	Action Taken [c] Other Action Taken [d] Outcome
Naldemedine 0.2 mg	Japan [redacted]	Male 64 48	Non-small cell lung cancer (lung cancer aggravated)	58 1 +	Severe Serious Not related	Not applicable No Fatal
Naldemedine 0.2 mg	Japan [redacted]	Male 64 50	Malignant neoplasm of unknown primary site (Carcinoma of unknown primary)	59 1 +	Severe Serious Not related	Not applicable No Fatal
Naldemedine 0.2 mg	Japan [redacted]	Male 64 71	Metastases to meninges (worsening of carcinomatous meningitis)	94 1 +	Severe Serious Not related	Not applicable No Fatal
Naldemedine 0.2 mg	Japan [redacted]	Male 60 25	Gastric cancer (Progression (Progression of gastric cancer)	26 1 +	Severe Serious Not related	Drug withdrawn No Fatal
Naldemedine 0.2 mg	Japan [redacted]	Male 76 75	Lung adenocarcinoma (Deterioration of Lung cancer)	76 1 +	Severe Serious Not related	Drug withdrawn Yes Fatal
Naldemedine 0.2 mg	Japan [redacted]	Male 66 29	Lung neoplasm malignant (Deterioration of Lung cancer)	38 1 +	Severe Serious Not related	Not applicable Yes Fatal
Naldemedine 0.2 mg	Japan [redacted]	Male 75 79	Pneumonia (Pneumonia)	72 18 +	Severe Serious Not related	Dose not changed Yes Fatal
			Lung neoplasm malignant (Aggravation of the underlying disease)	89 1 +	Severe Serious Not related	Not applicable No Fatal

Table 48 Subjects Who Died in Phase 2 and Phase 3 Studies in Subjects with Cancer and Opioid-induced Constipation (Continued)

Study Group	Region / Patient ID	Sex / Age (years) / Duration of Exposure (days)	Preferred Term (Reported Term)	Timing of Onset [a] / Duration [b]	Severity / Seriousness/ Causality	Action Taken [c] Other Action Taken [d] Outcome
Naldemedine 0.2 mg	Japan [redacted]	Male 75 15	Malignant neoplasm of pleura (aggravation of the underlying disease(Pleura cancer))	15 1+	Severe Serious Not related	Drug withdrawn No Fatal
			Chronic obstructive pulmonary disease (Chronic emphysema acute aggravated)	15 1+	Severe Serious Not related	Drug withdrawn Yes Fatal
Naldemedine 0.2 mg	Japan [redacted]	Male 66 49	Pancreatic carcinoma (Worsening of pancreatic cancer)	67 1+	Severe Serious Not related	Not applicable No Fatal
Naldemedine 0.2 mg	Japan [redacted]	Female 56 57	Inflammatory carcinoma of the breast (primary disease aggravated)	70 1+	Severe Serious Not related	Not applicable No Fatal
Naldemedine 0.2 mg	Japan [redacted]	Female 75 53	Pancreatic carcinoma (Primary disease (pancreatic cancer) aggravated)	72 1+	Severe Serious Not related	Not applicable No Fatal
Naldemedine 0.2 mg	Japan [redacted]	Male 61 22	Pleural mesothelioma malignant (Primary disease(malignant pleural mesothelioma) aggravated)	24 1+	Severe Serious Not related	Not applicable No Fatal

a Timing of Onset = (Date of onset) - (Date of initial dose of randomised drug) +1.

b Duration = (Date of outcome) - (Date of onset) +1. Plus sign shows that the adverse event did not recover and was not recovering until the day of outcome assessment.

c Action Taken = Action taken with study drug.

d Other Action Taken = Action taken with other than study drug.

MedDRA Version: V9222, 15.1; V9236, 16.1; V9237, 16.1.

Source: Study V9222, Section 14.3.3.1, Study V9236, Section 14.2.1, and Study V9237, Section 14.2.1.

In the Phase 2 and Phase 3 studies in subjects with cancer and OIC, 29 subjects died of whom 22 were treated with naldemedine. In the placebo-controlled studies V9222 and V9236, 7 subjects treated with naldemedine (2 subjects treated with naldemedine 0.1 mg, 3 subjects treated with naldemedine 0.2 mg, and 2 subjects treated with naldemedine 0.4 mg) and 7 subjects treated with placebo died. In Study V9222, 7 subjects died, 4 treated with naldemedine (2 subjects treated with naldemedine 0.1 mg and 2 subjects treated with naldemedine 0.4 mg) and 3 subjects treated with placebo. In Study V9236, 7 subjects died (3 treated with naldemedine 0.2 mg and 4 treated with placebo). In the open-label extension Study V9237, 15 subjects died. All deaths were considered by the investigator not related to study treatment. One subject, treated with naldemedine 0.2 mg, died of influenzal pneumonia and bacterial pneumonia. All other subjects died due to worsening of their primary disease.

Laboratory findings

Non-cancer and OIC

No meaningful changes from baseline over time were observed in either treatment group for any of the haematology parameters explored.

Cancer and OIC

In the Phase 2 and Phase 3 studies in subjects with cancer and OIC, no meaningful changes from baseline over time were observed in any treatment group for any of the haematology parameters explored.

Clinical Chemistry

Non-cancer and OIC

no meaningful changes from baseline over time were observed in either treatment group for any of the chemistry parameters explored.

The effect of naldemedine on testosterone levels in males and prolactin in all subjects was assessed in the naldemedine global placebo-controlled Phase 3 studies. In all 3 Phase 3 placebo-controlled studies, mean changes in total and free testosterone in males from baseline to the end of the study (12 weeks or 52 weeks) in the naldemedine group were small and not meaningfully different from those in the placebo group. Similarly, the mean changes in prolactin from baseline to end of study for the naldemedine group were small and not meaningfully different from the placebo group in any of the 3 Phase 3 studies, in the overall population or in subgroups by gender.

Cancer and OIC

No meaningful changes from baseline over time were observed in any treatment group for any of the clinical chemistry parameters explored.

Few subjects had values for chemistry tests meeting predefined limits and in the pooled placebo-controlled Phase 2 and Phase 3 studies (V9222 and V9236), results were generally similar for naldemedine 0.2 mg and for placebo.

Mean changes in prolactin from baseline to end of study for the naldemedine group were generally small.

Urinalysis

In the global placebo-controlled Phase 3 studies in subjects with chronic non-cancer pain and OIC, no meaningful changes from baseline over time were observed in either treatment group for any of the urinalysis parameters explored. Similarly in Phase 2 and Phase 3 studies in subjects with cancer and OIC, no meaningful changes from baseline over time were observed in urinalysis parameters.

Vital signs, Physical examination and Potential effects on QTc interval

Overall, irrespective of study, study population or length of observation no meaningful changes in vital signs (systolic blood pressure, diastolic blood pressure or heart rate) were observed. Likewise, overall no meaningful changes in physical examination findings were registered across the studies.

Overall, no indication of naldemedine having a possible QTc prolonging effect was detected. In the Phase 1 single-ascending-dose study, no effect of naldemedine on the QTc interval was detected. Likewise, in the thorough QTc study investigating 0.2 mg and 1 mg doses no effect of naldemedine on the QTc interval was detected. In a Phase 2b dose-finding study, 3 subjects in each of the 0.1 mg and 0.4 mg groups had an increase in QTc interval of >30 msec but none had an increase of >60 msec. Among subjects receiving 0.2 mg, no QTc changes were detected. In the Phase 3 studies, the QTc interval changes registered

among subjects treated with naldemedine were comparable to those registered among subjects treated with placebo.

Safety in special populations

Age

Non-cancer and OIC

Analyses of subgroups defined by age (< 40, ≥ 40 to < 65, ≥ 65, or ≥ 75 years) did not identify meaningful differences in the incidences of TEAEs between subgroups or between treatment groups within a subgroup in either the global placebo-controlled Phase 3 population up to 12 weeks or the global placebo-controlled Phase 2b and Phase 3 population. As for all subjects, the incidence of ADRs was higher in the naldemedine group than the placebo group in all subgroups except subjects ≥ 75 years of age.

Cancer and OIC

Analyses did not identify meaningful differences in the incidences of TEAEs between age subgroups. In all subgroups, the incidence of TEAEs for the pooled studies (V9222 and V9236) was higher in each naldemedine group than in the placebo group. Similarly, the incidence of ADRs and the incidence of TEAEs in the Gastrointestinal Disorders SOC and diarrhoea was higher in all naldemedine groups than the placebo group in all subgroups.

Overall, the safety profile of naldemedine did not appear to be meaningfully different in subgroups defined by age.

Sex

Non-cancer and OIC

Analyses of subgroups by sex did not identify meaningful differences in the incidences of TEAEs between subgroups or between treatment groups within a subgroup in either the global placebo-controlled Phase 3 population up to 12 weeks or the global placebo-controlled Phase 2b and Phase 3 population. As for all subjects, the incidence of ADRs and TEAEs in the Gastrointestinal Disorders SOC was higher in the naldemedine group than the placebo group in both males and females.

In the analyses of subgroups by sex, across all parameters assessed, female subjects in both groups tended to have a higher incidence of TEAEs relative to their male counterparts; however, the differences between treatment groups in both subgroups were generally consistent. Overall, the safety profile of naldemedine did not appear to be meaningfully different in males and females.

Cancer and OIC

Analyses did not identify meaningful differences in the incidences of TEAEs between males and females. In both subgroups, the incidence of TEAEs for the pooled studies (V9222 and V9236) was higher in each naldemedine group than in the placebo group. Similarly, the incidence of ADRs and the incidence of TEAE in the Gastrointestinal Disorders SOC and diarrhoea was higher in all naldemedine groups than the placebo group in both males and females.

Overall, the safety profile of naldemedine did not appear to be meaningfully different in males and females.

Race

All studies in subjects with cancer and OIC were performed in Japanese or Korean subjects and so no evaluation of the effects of naldemedine in different racial subgroups can be made in this population.

Non-cancer and OIC

In the analysis of subgroups by race, subgroups other than Black or African American and White were too small to conduct a proper assessment and no conclusions could be drawn. For Black or African American and White subjects, analyses by subgroup did not identify meaningful differences in the incidences of TEAEs between treatment groups within a subgroup in either the global placebo-controlled Phase 3 population up to 12 weeks or the global placebo-controlled Phase 2b and Phase 3 population. As for all subjects, the incidence of ADRs and TEAEs in the Gastrointestinal Disorders SOC was higher in the naldemedine group than the placebo group in both Black or African American and White subgroups.

In general, subjects of White race in both groups tended to have a higher incidence of TEAEs relative to subjects of Black or African American race; however, the differences between treatment groups in both subgroups were generally consistent. Overall, the safety profile of naldemedine did not appear to be meaningfully different in Black or African American and White subjects.

Body Mass Index

The effects of naldemedine were examined in subgroups of subjects with baseline BMI in the following categories: < 18.5, ≥ 18.5 to < 25.0, ≥ 25.0 to < 30.0, and ≥ 30 kg/m2.

Non-cancer and OIC

In the analyses of subgroups by BMI, the subgroup of subjects with BMI < 18.5 kg/m2 was too small to conduct a proper assessment and no conclusions could be drawn.

In the other subgroups by BMI, analyses did not identify meaningful differences in the incidences of TEAEs between subgroups or between treatment groups within a subgroup in either the global placebo-controlled Phase 3 population up to 12 weeks or the global placebo-controlled Phase 2b and Phase 3 population. As for all subjects, the incidence of ADRs and the incidence of TEAEs in the Gastrointestinal Disorders SOC was higher in the naldemedine group than the placebo group in all BMI subgroups.

No meaningful differences in the TEAE measures assessed were observed between subgroups or between treatment groups in any of the subgroups. Overall, the safety profile of naldemedine did not appear to be meaningfully different in subgroups defined by BMI.

Cancer and OIC

In the analyses of subgroups by BMI, the subgroup of subjects with BMI ≥ 30 kg/m2 was too small to conduct a proper assessment and no conclusions could be drawn.

Analyses did not identify meaningful differences in the incidences of TEAEs between BMI subgroups. In all subgroups the incidence of TEAEs for the pooled studies (V9222 and V9236) was higher in each naldemedine group than in the placebo group. Similarly, the incidence of ADRs and the incidence of TEAEs in the Gastrointestinal Disorders SOC and diarrhoea was higher in all naldemedine groups than the placebo group in all BMI subgroups.

Overall, the safety profile of naldemedine did not appear to be meaningfully different in subgroups defined by BMI.

Renal Insufficiency

A dedicated Phase 1 study with naldemedine was conducted in subjects with mild, moderate or severe renal impairment, in subjects with end-stage renal disease (ESRD) requiring haemodialysis (HD), and in healthy control subjects with normal renal function (Study V921B). Pharmacokinetic data from the study demonstrated that exposure (AUC) to naldemedine (and nor-naldemedine) in subjects with varying

degrees of renal impairment is not clinically meaningfully different from exposure in subjects with normal renal function. The pharmacokinetic (PK) data from this study provides an exposure-based rationale for the safe use of naldemedine in subjects with renal impairment without dose adjustment.

Importantly, in the global Phase 3 pooled population up to 12 weeks in subjects with chronic non-cancer pain and OIC, a safety analysis was conducted by subgroups defined by renal function status (based on eGFR values obtained at baseline, prior to randomisation). Incidences of TEAEs overall, TEAEs in the Gastrointestinal Disorders SOC, and specific TEAEs of “abdominal pain”, diarrhoea, nausea, and vomiting in subgroups defined by renal function status (normal, mild renal impairment, moderate renal impairment), were generally similar between subgroups and between treatment groups within each of the subgroups. The differences between treatment groups across all subgroups in these measures of TEAEs were generally consistent with the differences between groups observed for the overall pooled population. There were also no important differences between subgroups in the comparative incidences of ADRs for naldemedine and placebo, with a higher proportion of subjects reporting ADRs in the naldemedine group in each subgroup.

Hepatic Insufficiency

A dedicated Phase 1 study with naldemedine was conducted in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B) and healthy control subjects with normal hepatic function (Study V921C). Pharmacokinetic data from the study demonstrated that exposure (AUC) to naldemedine (and nor-naldemedine) in subjects with varying degrees of hepatic impairment is not clinically meaningfully different from exposures in subjects with normal hepatic function. The PK data from this study provide an exposure-based rationale for the safe use of naldemedine in subjects with mild or moderate hepatic impairment without dose adjustment. The PK of naldemedine has not been evaluated in subjects with severe hepatic impairment (Child-Pugh Class C), therefore, naldemedine should be avoided in this population.

Extrinsic factors

Subjects with and Inadequate Response to Laxatives

Non-cancer and OIC

Table 49 Duration of Treatment Exposure (in Days) by LIR/Non-LIR Subgroups (Studies V9231 and V9232) – Safety Population

	LIR		Non-LIR	
	Naldemedine 0.2 mg N=311	Placebo N=311	Naldemedine 0.2 mg N=220	Placebo N=226
N	311	311	220	226
Mean	78.0	78.0	76.6	77.8
SD	21.39	20.10	23.31	21.05
Min	1	1	1	1
Median	85.0	85.0	84.0	84.0
Max	99	108	120	100
Days	n (%)	n (%)	n (%)	n (%)
>=1 to <=14	19 (6.1)	10 (3.2)	16 (7.3)	11 (4.9)
>=15 to <=28	3 (1.0)	12 (3.9)	4 (1.8)	7 (3.1)
>=29 to <=56	8 (2.6)	11 (3.5)	6 (2.7)	6 (2.7)
>=57 to <=84	122 (39.2)	121 (38.9)	99 (45.0)	101 (44.7)
>=85	159 (51.1)	157 (50.5)	95 (43.2)	101 (44.7)

Duration of Exposure (days) = (Date of last dose of study drug) - (Date of initial dose of study drug) +1.

Source: CTD Section 5.3.5.3, Table 14.1.2-3-1a

Demographic and other baseline characteristics were generally consistent across LIR and non-LIR subgroups and treatment groups within subgroups for Studies V9231 and V9232. The mean age of subjects was 53.4 years in both subgroups. In the LIR subgroup 61.9% were female and 83.3% were White and in the non-LIR subgroup 58.1% were female and 76.7% were White. The proportion of subjects enrolled in the EU was higher for the LIR subgroup (15.4%) than for the non-LIR subgroup (12.1%). At baseline, there were no important differences in the number of subjects in each eGFR category between the treatment groups in either the LIR or non-LIR subgroups.

The average daily dose of opioids at baseline was generally consistent across subgroups and between treatment groups. For the LIR subgroup, the average daily dose of opioids was 116.94 mg morphine-equivalents for naldemedine and 127.18 mg morphine-equivalents for placebo and for the non-LIR subgroup it was 122.23 mg morphine-equivalents for naldemedine and 135.91 mg morphine-equivalents for placebo. These average doses were similar to those observed for the population overall (124.17 mg morphine-equivalents). The duration of opioid use prior to screening was slightly longer for LIR subjects (60.99 months) than for non-LIR subjects (58.78 months) but duration was similar for each treatment group within each subgroup. There were no important differences in concomitant medication use between LIR and non-LIR subgroups and between treatment groups within subgroups, including usage of opioids, CYP3A4 inhibitors, and P-gp inhibitors.

Table 50 Overall Summary of Treatment-emergent Adverse Events by LIR/Non-LIR Subgroups (Studies V9231 and V9232) – Safety Population

	LIR			Non-LIR		
	Naldemedine 0.2 mg N=311 n (%)	Placebo N=311 n (%)	Difference (95% CI) [a]	Naldemedine 0.2 mg N=220 n (%)	Placebo N=226 n (%)	Difference (95% CI) [a]
TEAEs	169 (54.3)	163 (52.4)	1.9 (-5.9, 9.8)	96 (43.6)	87 (38.5)	5.1 (-4.0, 14.3)
ADRs	69 (22.2)	53 (17.0)	5.1 (-1.1, 11.4)	42 (19.1)	22 (9.7)	9.4 (2.9, 15.8)
AEs Leading to Discontinuation	15 (4.8)	11 (3.5)	1.3 (-1.9, 4.4)	12 (5.5)	2 (0.9)	4.6 (1.3, 7.8)
SAEs except Deaths	14 (4.5)	12 (3.9)	0.6 (-2.5, 3.8)	8 (3.6)	5 (2.2)	1.4 (-1.7, 4.6)
SADRs	3 (1.0)	1 (0.3)	0.6 (-0.6, 1.9)	1 (0.5)	0	0.5 (-0.4, 1.3)
SAEs Leading to Discontinuation	3 (1.0)	3 (1.0)	0.0 (-1.5, 1.5)	3 (1.4)	0	1.4 (-0.2, 2.9)
Deaths	1 (0.3)	0	0.3 (-0.3, 1.0)	0	0	0.0 (---, ---)

CI : Confidence Interval

ADRs were defined as TEAEs that were considered by the Investigator to be definitely, probably, or possibly related to IMP.

SADRs were defined as serious ADRs.

[a] CIs based on normal approximation may not be reliable for small counts and should be interpreted with caution.

Source: CTD Section 5.3.5.3, Table 14.3-1.1-1a

Table 51 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term with ≥3% by LIR/Non-LIR Subgroups (Studies V9231 and V9232) – Safety Population

	LIR			Non-LIR		
System Organ Class - Preferred Term	Naldemedine 0.2 mg N=311 n (%)	Placebo N=311 n (%)	Difference (95% CI) [a]	Naldemedine 0.2 mg N=220 n (%)	Placebo N=226 n (%)	Difference (95% CI) [a]
Infections and infestations						
- Sinusitis	7 (2.3)	10 (3.2)	-1.0 (-3.5, 1.6)	1 (0.5)	3 (1.3)	-0.9 (-2.6, 0.9)
- Urinary tract infection	10 (3.2)	14 (4.5)	-1.3 (-4.3, 1.7)	3 (1.4)	7 (3.1)	-1.7 (-4.5, 1.0)
Gastrointestinal disorders						
- Abdominal pain	16 (5.1)	6 (1.9)	3.2 (0.3, 6.1)	15 (6.8)	2 (0.9)	5.9 (2.4, 9.5)
- Diarrhoea	22 (7.1)	11 (3.5)	3.5 (0.0, 7.0)	19 (8.6)	2 (0.9)	7.8 (3.8, 11.7)
- Nausea	14 (4.5)	9 (2.9)	1.6 (-1.4, 4.6)	11 (5.0)	7 (3.1)	1.9 (-1.8, 5.6)
Musculoskeletal and connective tissue disorders						
- Back pain	11 (3.5)	10 (3.2)	0.3 (-2.5, 3.2)	5 (2.3)	5 (2.2)	0.1 (-2.7, 2.8)

CI : Confidence Interval

MedDRA ver. 16.1

TEAEs with the same PT occurring more than once in a subject were counted once.

[a] CIs based on normal approximation may not be reliable for small counts and should be interpreted with caution.

Source: CTD Section 5.3.5.3, Table 14.3-1.2.3-1a

Table 52 Incidence of Adverse Drug Reactions by System Organ Class and Preferred Term with ≥1% by LIR/Non-LIR Subgroups (Studies V9231 and V9232) – Safety Population

	LIR			Non-LIR		
System Organ Class - Preferred Term	Naldemedine 0.2 mg N=311 n (%)	Placebo N=311 n (%)	Difference (95% CI) [a]	Naldemedine 0.2 mg N=220 n (%)	Placebo N=226 n (%)	Difference (95% CI) [a]
Nervous system disorders						
- Headache	4 (1.3)	2 (0.6)	0.6 (-0.9, 2.2)	1 (0.5)	2 (0.9)	-0.4 (-1.9, 1.1)
Gastrointestinal disorders						
- Abdominal distension	3 (1.0)	5 (1.6)	-0.6 (-2.4, 1.1)	2 (0.9)	2 (0.9)	0.0 (-1.7, 1.8)
- Abdominal pain	12 (3.9)	4 (1.3)	2.6 (0.1, 5.1)	14 (6.4)	2 (0.9)	5.5 (2.0, 8.9)
- Abdominal pain upper	4 (1.3)	0	1.3 (0.0, 2.5)	2 (0.9)	2 (0.9)	0.0 (-1.7, 1.8)
- Diarrhoea	17 (5.5)	6 (1.9)	3.5 (0.6, 6.5)	15 (6.8)	1 (0.4)	6.4 (2.9, 9.8)
- Flatulence	5 (1.6)	6 (1.9)	-0.3 (-2.4, 1.7)	3 (1.4)	5 (2.2)	-0.8 (-3.3, 1.6)
- Nausea	10 (3.2)	5 (1.6)	1.6 (-0.8, 4.0)	7 (3.2)	3 (1.3)	1.9 (-0.9, 4.6)
- Vomiting	5 (1.6)	3 (1.0)	0.6 (-1.1, 2.4)	2 (0.9)	0	0.9 (-0.3, 2.2)
Skin and subcutaneous tissue disorders						
- Hyperhidrosis	2 (0.6)	2 (0.6)	0.0 (-1.3, 1.3)	5 (2.3)	0	2.3 (0.3, 4.2)

CI : Confidence Interval
MedDRA ver. 16.1
ADRs with the same PT occurring more than once in a subject were counted once.
[a] CIs based on normal approximation may not be reliable for small counts and should be interpreted with caution.
Source: CTD Section 5.3.5.3, Table 14.3-1.4.2-1a

As for the global placebo-controlled Phase 3 population up to 12 weeks, in both LIR and non-LIR subgroups in the V9231 and V9232 population, the overall incidence of TEAEs was generally similar between treatments in both subgroups. Incidences of TEAEs by SOC were also generally similar between treatments in both subgroups, except for the Gastrointestinal Disorders SOC, in which the incidence of TEAEs was higher in the naldemedine treatment group compared with the placebo treatment group in both subgroups, with a difference between treatments of 6.8% (95% CI: 0.6, 13.0) in the LIR subgroup and 8.9% (95% CI: 2.3, 15.5) in the non-LIR subgroup.

However, the incidence of the TEAE (in particular GI disorders, abdominal pain and diarrhoea), of the ADR (in particular abdominal pain, diarrhoea and hyperhydrosis), AE leading to discontinuation (in particular GI disorders, abdominal pain and diarrhoea), and SAE leading to discontinuation was slightly higher in naldemedine than in placebo in non-LIR subgroup compared to LIR.

Table 53 Overall Summary of TEAE by LIR/Non-LIR Subgroups (Studies V9231 and V9232)– Safety Population

Non-Cancer and OIC patients	LIR		Non-LIR	
	Naldemedine 0.2mg	Placebo	Naldemedine 0.2mg	Placebo
Number of patients	311	311	220	226
TEAE incidence	54.3%	52.4%	43.6%	38.5%
GI disorders	22.8%	16.1%	19.5%	10.6%
Abdominal pain	5.1%	1.9%	6.8%	0.9%
Diarrhoea	7.1%	3.5%	8.6%	0.9%
ADR	22.2%	17%	19.1%	9.7%
Abdominal pain	3.9%	1.3%	6.4%	0.9%

Diarrhoea	5.5%	1.9%	6.8%	0.4%
Hyperhidrosis	0.6%	0.6%	2.3%	0
AE leading to discontinuation	4.8%	3.5%	5.5%	0.9%
GI disorders	3.5%	1.9%	3.2%	0.4%
Abdominal pain	1%	0.3%	1.8%	0.4%
Diarrhoea	1.6%	0.3%	1.8%	0
SAE leading to discontinuation	1%	1%	1.4%	0

No major differences were observed between non-LIR and LIR patients for the TEAE of special interest, SAE, SADR and deaths.

Cancer and OIC

Studies V9222 and V9236, the safety population comprised 257 LIR subjects and 47 non-LIR subjects. The safety profiles in LIR and non-LIR subgroups were in generally similar with the profile seen for subjects with chronic non-cancer pain and OIC.

However, the incidence of the TEAE (in particular GI disorders and diarrhoea), of the ADR, and of the AE leading to discontinuation was slightly higher in naldemedine than in placebo in non-LIR subgroup compared to LIR.

Table 54 Overall Summary of TEAE by LIR/Non-LIR Subgroups (Studies V9222 and V9236)– Safety Population

Cancer and OIC patients	LIR		Non-LIR	
	Naldemedine 0.2mg	Placebo	Naldemedine 0.2mg	Placebo
Number of patients	128	129	25	22
TEAE incidence	67.2%	55%	60%	22.7%
GI disorders	37.5%	26.4%	32%	4.5%
Diarrhoea	29.7%	18.6%	24%	0%
ADR	32.8%	24%	20%	4.5%
AE leading to discontinuation	4.7%	1.6%	20%	0

No major differences were observed between non-LIR and LIR patients for the SAE and deaths.

Opioid dose

Non-cancer and OIC

The number of subjects in the < 30 mg subgroup was too small to conduct a proper assessment and no conclusions could be drawn.

In the other subgroups by opioid dose, analyses did not identify meaningful differences in the incidences of TEAEs between treatment groups within a subgroup in either the global placebo-controlled Phase 3

population up to 12 weeks or the global placebo-controlled Phase 2b and Phase 3 population. As for all subjects, the incidence of TEAEs in the Gastrointestinal Disorders SOC and specific TEAEs of “abdominal pain”, diarrhoea, nausea, and vomiting was higher in the naldemedine group than the placebo group in all opioid dose subgroups.

Although numerically higher incidences of TEAEs, TEAEs in the Gastrointestinal Disorders SOC, and specific TEAEs of “abdominal pain”, diarrhoea, nausea, and vomiting were observed in subjects taking higher opioid doses compared to those taking lower doses, naldemedine was generally well tolerated regardless of the dose of opioid.

Overall, the safety profile of naldemedine did not appear to be meaningfully different in subgroups defined by opioid dose.

Cancer and OIC

In the analyses of subgroups by average daily dose of opioid at baseline, the subgroups of subjects with doses > 200 to ≤ 400 mg and > 400 mg were too small to conduct a proper assessment and no conclusions could be drawn.

For other subgroups, analyses did not identify meaningful differences in the incidences of TEAEs between opioid dose subgroups. In all subgroups, the incidence of TEAEs for the pooled studies (V9222 and V9236) was higher in each naldemedine group than in the placebo group. Similarly, the incidence of ADRs and the incidence of TEAEs in the Gastrointestinal Disorders SOC and of diarrhoea were higher in naldemedine groups than the placebo group in all subgroups.

Overall, the safety profile of naldemedine did not appear to be meaningfully different in subgroups defined by opioid dose.

CYP3A / P-gp inhibitors

Non-cancer and OIC

In the global placebo-controlled Phase 2b and Phase 3 pooled population, 133 (10.9%) subjects in the naldemedine group and 128 (10.4%) subjects in the placebo group were reported to have been taking a medication known to be a P-gp inhibitor at some point during the study. One hundred (8.2%) subjects in the naldemedine group and 85 (6.9%) subjects in the placebo group were reported to have been taking a medication known to be a moderate CYP3A inhibitor at some point during the study. Sixteen (1.3%) subjects in the naldemedine group and 18 (1.5%) subjects in the placebo group were reported to have been taking a medication known to be a strong CYP3A inhibitor, at some point during the study concomitantly with study drug. The number of subjects using strong CYP3A4 inhibitors was very small and so conclusions based on this subgroup must be interpreted with caution.

The incidences of TEAEs in subjects not using inhibitors was lower than in subjects using inhibitors (43.9% for naldemedine versus 43.1% for placebo for subjects not using inhibitors, 66.7% for naldemedine versus 61.0% for placebo for subjects using P-gp inhibitors, 69.2% for naldemedine versus 71.6% for placebo for subjects using moderate CYP3A inhibitors, and 100% for naldemedine versus 54.5% for placebo for subjects using strong CYP3A inhibitors for the global placebo-controlled Phase 3 population up to 12 weeks). For subjects using P-gp inhibitors and moderate CYP3A4 inhibitors, no meaningful differences in the incidences of TEAEs between treatment groups within a subgroup in either the global placebo-controlled Phase 3 population up to 12 weeks or the global placebo-controlled Phase 2b and Phase 3 population were observed. In subjects using a strong CYP3A4 inhibitor, the incidence of TEAEs was higher for naldemedine than for placebo.

In subgroups of subjects taking a P-gp inhibitor or a moderate CYP3A inhibitor concomitantly with study drug, differences between treatment groups in the incidence of TEAEs in the Gastrointestinal Disorders SOC, and specific TEAEs of “abdominal pain”, diarrhoea, nausea, and vomiting were generally consistent with those observed in subjects not taking these type of medications. In the subgroup of subjects taking strong CYP3A inhibitors, larger differences between treatment groups were observed in the incidence of TEAEs in the Gastrointestinal Disorders SOC, and specific TEAEs of abdominal pain, diarrhoea and nausea compared with those in subjects not taking any of these medications. These results are aligned with the PK results observed in drug-drug interaction studies and the expected change in the safety profile with exposure to higher concentrations of naldemedine.

Cancer and OIC

In the pooled population for Studies V9222 and V9236, 4 (7.1%) subjects in the naldemedine 0.1 mg group, 11 (7.1%) subjects in the naldemedine 0.2 mg group, 4 (7.1%) subjects in the naldemedine 0.4 mg group and 3 (2.0%) subjects in the placebo group were reported to have been taking a medication known to be a P-gp inhibitor at some point during the study. Five (8.9%) subjects in the naldemedine 0.1 mg group, 19 (12.3%) subjects in the naldemedine 0.2 mg group, 4 (7.1%) subjects in the naldemedine 0.4 mg group and 13 (8.6%) subjects in the placebo group were reported to have been taking a medication known to be a moderate CYP3A inhibitor at some point during the study. Two (3.6%) subjects in the naldemedine 0.1 mg group, 3 (1.9%) subjects in the naldemedine 0.2 mg group, 3 (5.4%) subjects in the naldemedine 0.4 mg group and 1 (0.7%) subjects in the placebo group were reported to have been taking a medication known to be a strong CYP3A inhibitor, at some point during the study concomitantly with study drug.

In the open-label Study V9237, 7 (5.3%) used P-gp inhibitors, 18 (13.7%) subjects used moderate CYP3A4 inhibitors, and 2 (1.5%) subjects used strong CYP3A4 inhibitors at some point during the study concomitantly with study drug. The number of subjects using all these inhibitors was very small and so conclusions based on these subgroups must be interpreted with caution. The majority of subjects were not using any inhibitors.

No pattern in the incidence of TEAEs was discernible in studies in subjects with cancer and OIC. The incidence of TEAEs in the Gastrointestinal Disorders SOC and of diarrhoea was numerically greater with naldemedine than with placebo for the pooled placebo-controlled studies (V9222 and V9236) for all subgroups. For the open-label study (V9237), the incidence of TEAEs in the Gastrointestinal Disorders SOC and diarrhoea was higher in subjects using no inhibitors than in the other subgroups. Due to the small number of subjects using inhibitors in subjects with cancer pain and OIC, it is not possible to draw any clear conclusions from these data.

Use in pregnancy and lactation

To date, no cases of naldemedine being administered to pregnant women have been reported. It is unknown whether naldemedine or its metabolites are excreted in human milk. No human data on the effect of naldemedine on fertility are available.

Immunological events

Hypersensitivity

In the naldemedine programme in studies in chronic non-cancer pain and OIC and cancer and OIC, one SADR of hypersensitivity that led to discontinuation was reported for Subject 10602-002 in the naldemedine group in Study V9231. No other ADRs of hypersensitivity or drug hypersensitivity were reported.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions

Concomitant use of naldemedine with strong CYP3A inducers such as rifampin, carbamazepine, phenytoin, and St John's wort are expected to decrease the exposure to naldemedine, which may reduce the clinical effectiveness and therefore, concomitant use of naldemedine with strong CYP3A inducers is not recommended. Concomitant use of naldemedine with strong CYP3A inhibitors such as itraconazole, clarithromycin and ketoconazole would be expected to increase the exposure of naldemedine, which may increase the risk for ADRs. Therefore, concomitant use with strong, but not moderate, CYP3A inhibitors should be avoided. Clinically meaningful drug interactions with P-gp inhibitors are not expected. Naldemedine also may be co-administered with gastric-acid reducing agents (H2-receptor blockers, proton pump inhibitors, antacids). In vitro studies have shown that there is no clinically relevant effect of naldemedine on other co-administered drugs.

Drug-food interactions

PK data did not indicate clinically relevant differences when naldemedine were administered under fed and fasting conditions. Naldemedine may be administered with or without food.

Interaction with opioid therapy

Although numerically higher incidences of TEAEs, TEAEs in the Gastrointestinal Disorders SOC, and specific TEAEs of "abdominal pain", diarrhoea, nausea, and vomiting were observed in subjects taking higher opioid doses compared to those taking lower doses, naldemedine was generally well tolerated regardless of the dose of opioid. Naldemedine was also generally well tolerated regardless of the type of opioid. In subjects in the methadone subgroup (which only included 49 [4.2%] subjects in the naldemedine group and 55 [4.7%] subjects in the placebo group), higher incidences of TEAEs overall, TEAEs in the Gastrointestinal Disorders SOC, and specific TEAEs of "abdominal pain," diarrhoea, nausea, and vomiting were reported compared with the other subgroups by opioid type, however, these events were generally mild to moderate in severity, short in duration and did not lead to discontinuation of study drug. Therefore, it is considered that naldemedine can be used without regard to the opioid type or the opioid dose. This is supported by preclinical data showing that naldemedine acts as a non-competitive antagonist at the μ-opioid receptor due to its slow association and disassociation kinetics, allowing naldemedine to maintain the antagonistic effect even when higher concentrations of the opioid are present.

Discontinuation due to adverse events

Non-cancer and OIC

In the global Phase 3 pooled population up to 12 weeks, TEAEs leading to discontinuation were consistently reported more frequently for subjects in the naldemedine group compared with subjects in the placebo group across the 3 studies and in the overall pooled population. In the overall pooled population, TEAEs leading to discontinuation were reported for 4.8% of subjects in the naldemedine group and 2.5% of subjects in the placebo group with a difference between groups of 2.3% (95% CI: 0.8, 3.8).

In general, the higher incidence of TEAEs leading to discontinuation in the naldemedine group compared with the placebo group was mainly due to a higher incidence of TEAEs leading to discontinuation in the Gastrointestinal Disorders SOC (37 [3.2%] subjects vs. 12 [1.0%] subjects, respectively; between-group difference 2.2%, 95% CI: 1.0, 3.3). In the Gastrointestinal Disorders SOC, the difference between groups

was driven by a higher frequency of TEAEs of abdominal pain, diarrhoea, nausea and vomiting that led to discontinuation.

Results were generally similar for the global placebo-controlled Phase 2b and Phase 3 population including the long-term Study V9235.

The rate of discontinuations with long-term treatment appeared to be generally similar to that observed with treatment up to 12 weeks.

Cancer and OIC

In the placebo-controlled Phase 2 and Phase 3 pooled population, the incidence of TEAEs leading to discontinuation was low and similar across naldemedine doses and higher in naldemedine groups than in the placebo group. There were 3 (5.4%) subjects in the naldemedine 0.1 mg group, 11 (7.1%) subjects in the naldemedine 0.2 mg group, 4 (7.1%) subjects in the naldemedine 0.4 mg group and 2 (1.3%) subjects in the placebo group who were reported to have had TEAEs leading to discontinuation. Twelve (9.2%) subjects in the open-label Study V9237 had TEAEs leading to discontinuation.

Post marketing experience

The Applicant contributes post-marketing data from Japan. From the date of marketing authorisation in Japan (7 June 2017) to 31 July, an estimated 4216 patients have been exposed to naldemedine. From 7 June to 22 September, spontaneous reporting has led to registration of a total of 358 events of AEs, 345 of which were non-serious. The majority, 337 AEs, belonged to the SOC of GI-disorders. By PT, diarrhoea was the most frequently reported AE with 262 cases being registered.

Further, reports of medication errors have been contributed. The majority of medication errors (44/51 valid cases) were due to inappropriate prescribing. No post-marketing data from the US are available.

2.6.1. Discussion on clinical safety

The number of included patients, the number of exposed patients, and the pooling strategy of the summary of clinical safety is overall considered acceptable.

Overall, the naldemedine-group and the placebo-group were comparable with regard to demographic characteristics. The non-cancer and OIC population represents the majority of the presumed target population. According to the EMA guideline (EMA/CHMP/336243/2013) this is considered acceptable even if an indication in the cancer and OIC population is applied for. Data from the non-cancer and OIC population can to an extent be extrapolated to the cancer and OIC population. A prerequisite for the extrapolation, according to the guideline is that a sufficiently large subgroup from the studies in non-cancer and OIC patients has been treated with high doses of opioids. Constipation related to opioid treatment is comparable irrespective of whether the pain is cause by underlying cancer or a non-malignant condition. Thus, extrapolation between groups is considered acceptable.

The proposed indication is to use naldemedine in adult patients with OIC irrespective of the underlying disease/state causing the need for opioid treatment. If this underlying disease is malignant disease (a cause which has also been included in the registration studies), it is very likely that such patients during the progression of their disease will lose weight which may eventually cause them to be underweight. The patients included in the cancer and OIC studies indeed have a much lower median BMI (20.2 kg/m^2) than the patients included in the non-cancer and OIC studies (30.3 kg/m^2). However, the cancer and OIC patients are few (n=131 exposed to naldemedine) compared with the non-cancer and OIC patients (n=1163 exposed to naldemedine). The observed bodyweight and BMI difference may be due to ethnic differences in the populations included rather than a priori skewed inclusion. Further, it appears that no

uniform pattern with regard to treatment difference between active intervention and placebo with regard to AEs exists when stratified by BMI groups. A true underlying weight effect would be expected to yield a similar AE pattern in both populations. Additionally, the assumption that no clinically meaningful effect of weight is present is further supported by the population PK analysis.

With regard to opioid consumption at baseline, it is striking that the cancer and OIC population has lower than anticipated doses of opioids at baseline. This is in contrast to expectations as patients suffering from malignant diseases usually have a higher opioid consumption than patients with non-cancer. A similar safety profile of naldemedine when patients are treated with similar doses of opioids, irrespective of whether or not the patients have cancer can be expected.

With regard to types of cancer represented in the studies of Cancer and OIC, the most common types appear represented among study participants. Thus, the study population seems comparable with the target population. This is equally the case with regard to concomitant medication in a population with malignant disease.

Irrespective of population and subgroup, naldemedine-treated patients have an increased incidence of TEAEs belonging to the SOC of GI Disorders. Given the mechanism of action of naldemedine, it seems plausible that there is a causal relationship between administration of naldemedine and GI AEs. It is considered reassuring that the majority of these AEs were of mild to moderate severity and that there were no GI SAEs. Generally, a dose-response relationship was observed and AEs typically occurred early during the course of study.

Within the Cancer and OIC population, however, there was also an increased incidence of TEAEs belonging to the SOC of Metabolism and Nutritional Disorders. This was driven by an increased frequency of Decreased appetite for which a dose-response relationship seemed indicated when pooling studies V9222 and V9236 (NAL 0.1 mg: 5.4%; NAL 0.2 mg: 5.8%; NAL 0.4 mg: 10.7%; PBO: 1.3%). In study V9237, the incidence of Decreased appetite was 10.7%. Patients with malignant disease may at baseline be at risk of experiencing difficulties maintaining a normal body weight and in the event of Decreased appetite, a tendency towards weight loss may be augmented. However, most events of Decreased Appetite were rated of mild severity and only 2 patients discontinued due to this AE. Overall, no apparent safety signal regarding Decreased Appetite has been identified.

Overall, the number of Liver Events and Major Adverse Cardiovascular Events was low and comparable between naldemedine-treated and placebo-treated patients. No specific safety signal was detected. With regard to Opioid Withdrawal Adverse Events, Effect on Centrally Mediated Analgesia and Change in Opioid Dose, populations and subgroups were also overall comparable. However, 7/8 patients with Cancer and OIC, who had symptoms of opioid withdrawal, had non-GI opioid withdrawal symptoms. A relevant warning regarding the use of naldemedine in patients with disruptions to the blood-brain barrier is included in section 4.4 of the proposed SmPC.

Overall, in the non-cancer and OIC population (global placebo-controlled phase 3 up to first 12 weeks), with naldemedine 0.2 mg compared to placebo, a slightly higher number of opioid withdrawal (10 subjects - 0.9% and 6 subjects - 0.5%, respectively) and an higher number of possible opioid withdrawal (14 subjects - 1.2% and 3 subjects - 0.3%, respectively) were reported. These trends are confirmed in the global placebo-controlled Phase 2b and Phase 3 population (including the long-term Study V9235). In cancer and OIC patients however, with naldemedine 0.2 mg compared to placebo, the number of patients with opioid withdrawal is similar (0 in both arms), and so for the number of patients with possible opioid withdrawal (1 in naldemedine 0.2 mg and 0 in placebo); however, the total number of treated cancer and OIC patients was much lower than the total number of treated non-cancer and OIC patients. Particularly, it was questioned whether a safety signal was present regarding patients treated with methadone. Based on the data presented, it is agreed that no safety signal appears evident when comparing opioid

withdrawal and possible opioid withdrawal in patients taking methadone with those who took other opioids. However, “Effect of concurrent methadone use” has been added as an area of missing information in the RMP.

There were no events of GI perforation and no reports of overdose in subjects with OIC treated with naldemedine during the study. The use of naldemedine in patients with known or suspected gastrointestinal obstruction or patients at increased risk of recurrent obstruction is contraindicated due to the potential for gastrointestinal perforation. Further, section 4.4 of the SmPC contains a warning regarding use in patients with GI malignancies included in the section regarding gastrointestinal perforation. The potential for drug abuse of naldemedine is considered low, no withdrawal or rebound effects were observed, and naldemedine had no impact on the ability to drive or operate machinery or impairment of mental ability.

The incidence of SAEs was overall low and comparable between treatment groups. The indication of a dose-response relationship was uncertain and no specific signs of a safety signal were evident. Overall, 39 patients died during the study. No deaths were considered related to study treatment by the investigators and no particular pattern of cause of death was evident. Deaths were balanced between naldemedine-treated and placebo-treated groups in the placebo-controlled studies.

With regard to Laboratory Findings, no specific observations were made for either haematology, clinical chemistry or urinalysis. In particular, no evidence of changes in prolactin levels were observed in the Phase 2 and 3 studies, and observations did not indicate that naldemedine has an effect on testosterone levels in humans. Vital signs and Physical examinations did not reveal meaningful changes over the course of the study. There is no available data which indicate that naldemedine causes prolongation of the QTc interval. It is noted that matched concentrations-ECG data were not available in the global placebo-controlled Phase 3 studies in subjects with chronic non-cancer pain and OIC and that, when available, ECG and plasma concentration data were not informative for C-QT modelling.

All three opioid receptor subtypes (mu-, delta- and kappa-) are present in the heart. As such, cardio-protective effects of endogenous opioids, particularly related to delta opioid receptors (for which naldemedine has receptor antagonist activity) have been widely studied. Systemic exposure to opioid receptor blockade could theoretically antagonize an endogenous opioid mediated cardio-protective system. The concern for a potentially increased risk of Major Adverse Cardiovascular Events (MACE) with PAMORAs as a pharmacological class will be addressed through routine pharmacovigilance activities, a retrospective cohort study, a post-marketing observational epidemiologic study (requested by the FDA) by addition to the RMP that patients at high risk of cardiovascular events were not included in the clinical development programme, and by addition of a warning to section 4.4 of the SmPC advising caution in patients at high risk of cardiovascular events.

With regard to Age, Sex, Race, Renal Insufficiency and Hepatic Insufficiency populations and subgroups were overall comparable with no indication of an increased incidence of AEs based on these characteristics.

With regard to LIR/non-LIR status, the pattern of TEAEs was overall comparable between groups. When stratified by LIR/non-LIR, treatment groups were overall comparable with regard to completion of the study and duration of exposure. However, in the cancer and OIC population, the incidence of TEAEs leading to discontinuation was higher in the naldemedine group than in the placebo group in both LIR and non-LIR subgroups. An updated analysis of causes and severity of TEAEs leading to study treatment interruption and study treatment discontinuation has been submitted. This has not yielded any further safety signals.

With regard to age, sex, race, region, renal function, average daily dose of opioids, duration of opioid treatment and concomitant medication use including usage of opioids, CYP3A4 inhibitors and P-gp inhibitors, groups stratified by LIR/non-LIR were overall also comparable. With regard to TEAEs by LIR/non-LIR, overall ADRs was registered significantly more often among naldemedine-treated patients as compared to placebo-treated non-LIR patients while there was a numerical difference disfavouring naldemedine with regard to the same parameter among LIR patients. Further, the pattern of onset of TEAEs was similar between subgroups and consistent with that of the overall population. Some minor differences were observed but the clinical relevance is questioned.

There were no meaningful differences when stratified by LIR/non-LIR with regard to chemistry tests, demographic characteristics. In total, 258 patients were assessed as LIR as compared to 47 patients assessed as non-LIR. Approximately 50% in each group were treated with naldemedine. Overall, the subgroups are considered sufficiently large to permit evaluation.

By Average total daily opioid dose at baseline and Region, no meaningful differences appear evident based on the presented documentation.

Naldemedine is metabolized by CYP3A4 and is a substrate for P-gp. Section 4.4 of the SmPC appropriately contains a warning regarding concomitant use of naldemedine and strong CYP3A4 inhibitors and inhibitors. With regard to drug-food interactions, no significant changes in AUC were observed when administration followed a high-fat meal. Regardless of the dose of opioid at baseline, naldemedine was generally well tolerated. Further, a warning regarding concomitant use of strong CYP3A inhibitors and inducers has been included in the SmPC.

With regard to fertility, pregnancy and lactation no human data are available. Animal data do not suggest an adverse effect on fertility and pregnancy. Thus, the SmPC appropriately recommends only to use naldemedine during pregnancy if the potential benefit to the mother justifies the potential risk to the foetus. However, animal studies indicate that naldemedine is excreted in milk. Based on this, although no human data are available, the SmPC states that use of naldemedine in breast-feeding mothers is not recommended. The Applicant speculates that 14 days would represent a safe period between last administration of naldemedine and re-initiation of breast-feeding. This consideration, however, remains theoretical.

Only subjects of Asian origin participated in the cancer and OIC studies. As has been discussed previously, the consumption of opioids at baseline of these patients is remarkably low.

During the naldemedine study program, one event of hypersensitivity was recorded. The narrative of this patient reveals that the individual had anamnestic events of hypersensitivity, allergy and anaphylactic events. Thus, the individual seems predisposed for allergic reactions. Overall, the naldemedine study program indicates a low risk of hypersensitivity associated with naldemedine treatment. In the SmPC, hypersensitivity to naldemedine (or excipients) is adequately listed as a contraindication in Section 4.3. Further, hypersensitivity is listed in Section 4.8 as an observed AE occurring with rare frequency (≥1/10,000 to <1/1,000).

The majority of AEs leading to discontinuation were considered related to study treatment. Most were reported as being of mild to moderate severity (although five events of abdominal pain leading to discontinuation were considered severe), most were of short duration and resolved after discontinuation of study treatment. Similar results were observed in the Global Placebo-controlled Phase 2b and 3 Population. TEAEs leading to interruption were specifically analysed and this yielded no specific safety signal.

Post-marketing data from the US are not yet available, but the applicant has provided post-marketing data from Japan. These are overall in accordance with expectations based on the safety profile of

naldemedine established during the clinical trials

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of naldemedine is considered acceptable. Based on the mechanism of action of naldemedine, a higher incidence of AEs belonging to the SOC of GI Disorders is in line with expectations.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Abdominal pain, diarrhoea and vomiting Opioid withdrawal syndrome
Important potential risks	Gastrointestinal perforation Anti-analgesic effect due to centrally-mediated opioid receptor antagonism
Missing information	Long-term use (more than 1 year) safety Patients with severe hepatic impairment Use in children Use in pregnant or breast-feeding women Patients at high risk of cardiovascular events Patients aged 75 years and older Patients with severe renal impairment Effect of concurrent methadone use

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Retrospective database cohort study An Observational	The primary objective of this post-authorisation safety study is to assess the incidence risk of major cardiovascular (CV)	• gastrointestinal perforation • abdominal pain	Study initiation:	31 Jan 2020
			Progress reports:	To be provided annually

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Post-Authorization Safety Study (PASS) of Patients with Chronic Opioid Use for Non-Cancer and Cancer Pain who have Opioid-Induced Constipation (OIC) Planned	outcomes (i.e. acute myocardial infarction, stroke, CV death) and gastrointestinal (GI) perforation, and to characterise the safety profile of naldemedine in routine clinical practice for the treatment of OIC in patients with chronic opioid use for non-cancer and cancer pain, both overall and for population subgroups under-represented in the clinical development programme	• diarrhoea • vomiting • opioid withdrawal syndrome • anti-analgesic effect of naldemedine • patients with severe hepatic impairment • patients at high risk of cardiovascular events • patients aged 75 years and over • use in children • use in pregnant women • patients with severe renal impairment • effect of concurrent methadone use • Long-term use (more than 1 year) safety		beginning one year following the start of data collection First report: 31 Jan 2021
			Interim reports:	To be provided with the progress reports every two years
			Final study report:	To be provided within 12 months of the end of data collection 31 Jan 2026

Risk minimisation measures

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Abdominal pain, diarrhoea and vomiting	Routine risk minimisation measures: • *Listed as adverse reactions in SmPC section 4.8* • *Listed as side effects in PL section 4* • *Warning in SmPC section 4.4 for the patient to report severe reactions to their physician for monitoring and treatment as needed* • *Warning in PL section 2 for the patient to report severe diarrhoea or stomach ache to their doctor for monitoring and treatment if needed* • *Guidance in SmPC section 4.9 that dose-dependent gastrointestinal reactions have occurred in overdose and to provide appropriate supportive care* • *Legal status (prescription only medicine)*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Retrospective database cohort study*

	Additional risk minimisation measures: • *None*	
Opioid withdrawal syndrome	Routine risk minimisation measures: • *Listed as an adverse reaction in SmPC section 4.8* • *Listed as a side effect in PL section 4* • *Warning in SmPC section 4.4 for the patient to discontinue naldemedine and to contact their physician if opioid withdrawal occurs* • *Warning in PL section 2 for the patient to contact their doctor and stop taking naldemedine should they develop opioid withdrawal symptoms* • *Warning in PL section 4 for the patient to stop taking naldemedine and to contact their doctor if they get a combination of 3 or more symptoms of opioid withdrawal syndrome on the same day* • *Warning in SmPC section 4.4 to consider the overall benefit-risk of naldemedine in patients with disruptions to the blood-brain barrier and to closely monitor symptoms* • *Warning in PL section 2 for the patient to talk to their doctor before taking naldemedine if they have cancer of the brain or central nervous system, multiple sclerosis, or Alzheimer's disease and to contact their doctor immediately if they develop opioid withdrawal symptoms* • *Guidance in SmPC section 4.6 about the risk of opioid withdrawal in the foetus following exposure in utero and a recommendation for use during pregnancy* • *Guidance in SmPC section 4.6 about the risk of opioid withdrawal*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Retrospective database cohort study*

	in the breast-fed infant and guidance for use during breastfeeding • *Guidance in PL section 2 for the patient to ask for advice if they are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby before taking naldemedine* • *Guidance in SmPC section 4.9 to provide appropriate supportive care in the case of overdose and to monitor for opioid withdrawal syndrome* • *Guidance in PL section 3 for the patient to contact their doctor or go to hospital if they have taken more naldemedine than they should* • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*	
Gastrointestinal perforation	Routine risk minimisation measures: • *Contraindication in SmPC section 4.3 for patients with or at risk of gastrointestinal perforation* • *Warning in PL section 2 for the patient not to take naldemedine if their bowel is blocked or perforated, or there is a high risk of their bowel becoming blocked as this may cause a hole in their bowel wall* • *Warning in SmPC section 4.4 for the overall risk-benefit of naldemedine to be considered in patients with impaired integrity of the gastrointestinal tract wall, that patients should be monitored and to discontinue naldemedine if gastrointestinal perforation is suspected* • *Warning in PL section 2 for the patient to talk to their doctor or pharmacist before taking naldemedine if they suffer from a disease which may affect their bowel wall* • *Warning in PL section 2 for*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Follow-up form for gastrointestinal Perforation* Additional pharmacovigilance activities: • *Retrospective database cohort study*

	the patient to talk to their doctor immediately and to stop taking naldemedine if they develop severe, lasting or worsening stomach pain as this could be a symptom of developing a hole in their bowel wall • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*	
Anti-analgesic effect due to centrally-mediated opioid receptor antagonism	Routine risk minimisation measures: • *Warning in SmPC section 4.4 for the overall benefit-risk of naldemedine to be considered in patients with disruptions to the blood-brain barrier because of possible reduced analgesia* • *Warning in PL section 2 for the patient to talk to their doctor before taking naldemedine if they have cancer of the brain or central nervous system, multiple sclerosis, or Alzheimer's disease and to contact their doctor immediately if the opioid medicine no longer controls their pain* • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Review of cases suggestive of a change in pain or a change in dose in the post-marketing setting indicative of a reduced analgesic effect of naldemedine* Additional pharmacovigilance activities: • *Retrospective database cohort study*
Long-term use (more than 1 year) safety	Routine risk minimisation measures: • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Retrospective database cohort study*
Patients with severe hepatic impairment	Routine risk minimisation measures: • *Guidance in SmPC section 4.2 that use of naldemedine in patients with severe hepatic impairment is not*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None*

	recommended • *Guidance in PL section 2 that the patient should talk to their doctor or pharmacist before taking naldemedine if they have severe liver disease such as alcoholic liver disease, viral liver infection or impaired liver function* • *Warning in SmPC section 4.4 that naldemedine has not been studied in patients with severe hepatic impairment and that use in these patients is not recommended* • *Information in SmPC section 5.2 that the effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of naldemedine was not evaluated* • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*	Additional pharmacovigilance activities: • *Retrospective database cohort study*
Use in children	Routine risk minimisation measures: • *Guidance in SmPC section 4.1 on the indicated population which specifies use in adults* • *Guidance in PL section 1 on the intended use of naldemedine in adult patients* • *Guidance in SmPC section 4.2 that the safety and efficacy of naldemedine in children and adolescents have not been established and that no data are available* • *Guidance in PL section 2 that naldemedine is not for children or adolescents because the effects in children and adolescents are not known* • *Information in SmPC section 5.2 that the pharmacokinetics of naldemedine in the paediatric population has not been studied* • *Legal status (prescription only medicine)*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *None*

	Additional risk minimisation measures: • *None*	
Use in pregnant or breast-feeding women	Routine risk minimisation measures: • *Guidance in SmPC section 4.6 about the risk of opioid withdrawal in the foetus following exposure in utero and a recommendation for use during pregnancy* • *Guidance in SmPC section 4.6 about the risk of opioid withdrawal in the breast-fed infant and guidance for use during breastfeeding* • *Guidance in PL section 2 for the patient to ask for advice if they are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby before taking naldemedine* • *Information in SmPC section 5.3 relating to in vivo findings concerning embryo-fetal development* • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Follow-up form for pregnancy* Additional pharmacovigilance activities: • *Retrospective database cohort study*
Patients at high risk of cardiovascular events	Routine risk minimisation measures: • *Warning in SmPC section 4.4 that patients with a recent history of myocardial infarction, stroke or transient ischaemic attack were not studied and these patients should be clinically monitored when taking naldemedine* • *Guidance in PL section 2 for the patient to talk to their doctor or pharmacist before taking naldemedine if they have had a heart attack within the last 3 months or if they have other severe heart problems* • *Legal status (prescription only medicine)*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Retrospective database cohort study*

	Additional risk minimisation measures: • *None*	
Patients aged 75 years and older	Routine risk minimisation measures: • *Guidance in SmPC section 4.2 that naldemedine should be initiated with caution in patients 75 years old and older due to limited therapeutic experience* • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Retrospective database cohort study*
Patients with severe renal impairment	Routine risk minimisation measures: • *Guidance in SmPC section 4.2 that use of naldemedine in patients with severe renal impairment is limited and therefore patients should be clinically monitored when initiating naldemedine* • *Information in SmPC section 5.2 that the pharmacokinetics of naldemedine is similar in patients with mild, moderate or severe renal impairment, patients with ESRD requiring haemodialysis and healthy subjects* • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Retrospective database cohort study*
Effect of concurrent methadone use	Routine risk minimisation measures: • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Retrospective database cohort study*

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of naldemedine with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers naldemedine to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Rizmoic (naldemedine) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Opioid-induced constipation (OIC) is the most common adverse drug reaction (ADR) occurring with the chronic use of opioids. With the treatment of naldemedine, the aim is to reverse the opioid induced constipation as naldemedine acts as an antagonist at the peripheral μ-, δ-, and κ-opioid receptors.

The aim of the therapy is to selectively interfere with opioid binding onto μ-opioid receptors in the gut, which are responsible for OIC, without interfering with the central analgesic effects of these opioids. Naldemedine was developed as a derivative of naltrexone to have a reduced ability to cross the Blood Brain Barrier and negligible CNS penetration at the recommended dose.

3.1.2. Available therapies and unmet medical need

There are a range of medicinal products and approaches currently available for the treatment of OIC. Standard laxatives are used as a first line therapy in OIC as they are widely available and often without medical prescription. However, many standard laxatives are not effective in treating the constipation caused by opioids. Other currently available peripherally-acting μ-opioid receptor antagonist (PAMORAs) include methylnaltrexone bromide (Relistor) and naloxegol (Moventig) which have been approved in the EU for the treatment of OIC.

Relistor (methylnaltrexone) is indicated for the treatment of opioid-induced constipation when response to laxative therapy has not been sufficient in adult patients, aged 18 years and older. It is administered subcutaneously. Moventig (naloxegol) is an oral therapy indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s).

Currently, there is no PAMORA approved in the EU for first line treatment.

3.1.3. Main clinical studies

There were four pivotal studies evaluating efficacy and safety of naldemedine 0.2 mg QD on the treatment of opioid induced constipation, three in non-cancer pain patients, V9231 (n=547), V9232 (n=553), V9235 (n=1246), and one in cancer pain patients, V9236 (n=193). All studies were randomised, double-blind, and placebo controlled. The cancer pain study only included patients from Japan. The two studies V9231 and V9232 in non-cancer patients investigated the efficacy of naldemedine over a 12 week treatment period, the study in cancer patients investigated the efficacy of naldemedine over a 2 week period, and study V9235 investigated the efficacy of naldemedine over a 52 week treatment period.

Patients in the cancer study, V9236, could enrol in a long-term open label safety follow up study (V9237).

3.2. Favourable effects

Primary endpoint SBM response rates

Non-cancer pain OIC patients

In all the studies V9231, V9232 and V9236, with SBM responder rates as primary endpoint treatment with naldemedine, resulted in a significantly larger proportion of SBM responders than treatment with placebo.

For the studies V9231 and V9232, SBM responders were defined as at least 3 SBMs/week with at least 1 SBM/week increase over baseline for at least 9 out of 12 weeks and at least 3 of the last 4 weeks. The treatment differences were 13.0% and 18.9%, respectively.

Pooled data for the primary efficacy endpoint for studies V9231 and V9232 show a difference of 16% in SBM responder rate of naldemedine 0.2 mg QD over placebo (95% CI 10;22). Similarly, pooled data showed a difference of 12% in CSBM responder rate in favour of naldemedine over placebo (95% CI 7; 17). The long-term study V9235 confirmed the long-term efficacy of naldemedine.

Subgroup analysis of the treatment effect, including age, gender, opioid dose (low/high), opioid type and BMI, overall, show a superior effect, as measured as SBM responder rate, vs placebo.

Cancer pain OIC patients

For study V9236 (cancer), SBM responders were defined as at least 3 SBMs/week and an increase in frequency of SBM from baseline of at least 1 SBM/week during the 2-week treatment period. The treatment differences was 36.8%. Similarly, a difference in CSBM responder rate in favour of naldemedine versus placebo of 29% was reported (95% CI 20, 39). Long-term efficacy was shown in a 12 week follow-up study (V9237).

LIR/non-LIR subgroup

The responder rates for naldemedine for both SBM and CSBM were similar in the post-hoc defined LIR and non-LIR subgroups, and generally consistent with the overall responder rates. The corresponding subgroups defined by the applicant (pooled groups from studies V9231 and V9232) are very similar in their baseline characteristics, and show almost identical difference in SBM responder rate of treatment vs placebo, i.e. 16.2% (95% CI 8.7,23.7) and 15.6% (95% CI 6.4,24.7) for the LIR and non-LIR groups, respectively. For the pool of the non-cancer studies V9231 and V9232, the efficacy results or the secondary endpoints consistently showed very similar treatment effects in both the LIR and non-LIR subgroups. Strictly laxative naïve patients have not been studied. Two groups of virtually laxative naïve subjects were defined post hoc consisting of subjects either laxative naïve up to first dose or laxative naïve up to screening. For both these groups, the treatment effect of naldemedine compared to placebo was clinically relevant at 13.6% and 17.3%, however it was only statistically significant in the last group, due to the small size of the first group.

Treatment failure with standard laxatives is a common problem in OIC, as it is also acknowledged in the concerned EMA guideline, which recommends to investigate medicinal products for OIC treatment in non-treated patients and laxative inadequate responders.

PK

In DDI studies concomitant use of naldemedine with strong CYP3A inducers induced a decrease in naldemedine exposure and may reduce the efficacy of naldemedine. Therfore concomitant use with strong CYP3A inducers is not recommended (see SmPC sections 4.4 and 4.5).

3.3. Uncertainties and limitations about favourable effects

In studies V9235 and V9236, treatment with naldemedine was investigated both as monotherapy and as add-on to laxatives. In study V9235, naldemedine, as add-on to laxatives, showed a similar treatment effect to the overall treatment effect, whereas for subjects not on a stable laxative regimen, there was a clear 12-week effect of naldemedine for all subjects, but no clear evidence of an effect beyond 12 weeks. In study V9236, the responder rates in the naldemedine group were similar regardless of laxative use (70.8% with laxatives vs. 72.0% without laxatives), but the responder rates in the placebo group differed substantially (39.2% with laxatives vs. 18.2% without laxatives); hence the respective treatment effects

were 31.6% with laxatives vs. 53.8% without laxatives. Thus, naldemedine had variable effect according to laxative use, but showed superior efficacy in both groups.

In studies V9231 and V9232, at least 4 days of diary entries related to defecation per week were necessary in order for that week to be evaluable. Sensitivity analyses performed with the choice of either 3 or 5 days instead resulted in very similar results.

In studies V9231, V9232, and V9235, the method for computing number of SBMs/BMs per week implicitly assumes that days with diary entry related to defecation are representative of days without diary entry related to defecation, which does not seem to be a reasonable assumption. However, in subsequent analyses where missing entries were regarded as 0 (bowel movements) (and the corresponding week not considered non-evaluable in spite of missing entries) naldemedine was consistently statistically superior to placebo. Similar results were obtained in a number of sensitivity analyses applying a range of different definitions of how to handle missing values (including a worst case scenario where weeks which had any number of missing entries of bowel movements were regarded as a non-response week). These additional analyses were considered demonstrating the robustness of results.

The main phase of the cancer pain OIC study was limited to two weeks instead of 4 weeks as recommended in the concerned EMA guideline. However, considering the demonstrated efficacy in the non-cancer population and the very strict primary and secondary endpoints the data can be considered sufficiently supportive. Furthermore a 12 week follow up study assessing safety and efficacy in this patient population was provided.

Baseline opioid levels in the non-cancer pain OIC trials V9231/V9232 and cancer pain OIC trials V9222/V9236 were not in line with expected ranges based on the concerned EMA guideline. In fact, only 25% of the Japanese cancer pain OIC patients were on high dose opioids compared with 43% of EU/US non-cancer pain patients. Overall, there is limited information regarding the efficacy in patient treated with more than 400 morphine-equivalent dose (MED) and thus it is uncertain wether 0.2 mg naldemedine would be effective in patients treated with more than 400 mg MED. As naldemedine must be considered a competitive antagonist, there is an upper limit of opioids where 0.2 mg naldemedine will no longer be effective. This uncertainty has been adequately addressed in the SmPC section 4.2 outlining that there is limited experience in patients treated with opioid doses higher thant 400mg morphine equivalent.

Subgroups

For the cancer studies, there were only few subjects in the two subgroups with BMI (≥30) and age (<40), respectively. Thus, in these subgroups, the treatment effect of naldemedine is uncertain. However, there is no reason to expect the treatment effect in these subgroups to differ substantially from the overall treatment effect.

For the non-cancer studies, treatment effect of naldemedine was consistent across subgroups of categorised average TDD, however only very few subjects received more than 400 mg MED. For the cancer studies, only two subgroup of average TDD (>30 to ≤100) and (>100 to ≤200) had a size sufficient large for meaningful comparisons; thus, the study gives no information about subjects receiving high opioid doses. It is, however, reasonable to expect that the effect observed in the non-cancer patients treated with up to 400 mg MED also apply to cancer patients. Overall, there is limited experience in patients received more than 400 mg MED and this is adequately addressed in the SmPC.

In the Black/African American subgroup of patients with non-cancer pain OIC, the response in the naldemedine arm compared to placebo overall is non-existing, mainly because of high placebo response in both pivotal trials and an absolute lack of efficacy of naldemedine in this patient subgroup in trial V9132 (n = 102 and n = 87 for pooled treatment and placebo arms). Further analysis lead to the conclusion that this was most probably a chance finding. There is no reason to believe that naldemedine should be less

effective in the Black/African American subgroup of patients considering that presence and function of μ-opioid receptors is similar regardless of racial origin, and PK data do not point to differences with the White subgroup of patients. Consequently, any mentioning of potential ethnic differences is not considered necessary.

LIR / non-LIR

The clinical program was not designed to discriminate between LIR and non-LIR patients. To address this issue, the applicant defined post-hoc criteria to define LIR and non-LIR patient groups. The definition of the LIR subgroup is not according to the EMA guideline, as the clinical development program was designed prior to the guideline. The post-hoc definition of the LIR and non-LIR subgroups aimed to align with the EMA guideline to the extent possible given the information available. Furthermore, efficacy has been demonstrated by showing consistent results in both LIR and non-LIR subgroups based on varying definitions of non-LIR, including two post-hoc definitions of subjects who can be considered to be "virtually" laxative naïve (strictly laxative naïve patients have not been studied). The LIR and the non-LIR subgroups were defined post-hoc and the individual trials were not powered to show treatment effect separately in these subgroups. However, for the pool of the two identically designed trials, V9231 and V9232, the subgroups were large enough to consistently show similar statistically significant treatment differences in responder proportions in the LIR and the non-LIR subgroups. Both studies had a 12-week treatment period and the primary endpoint was the proportion of responders as required by the EMA guideline, and the definition of a responder was in-line with the guideline.

For the pool of trials V9231 and V9232, the efficacy results on the secondary endpoints consistently showed very similar treatment effects in the LIR and non-LIR subgroups. Thus, it has been demonstrated that, for the non-cancer trials, the efficacy in the LIR and the non-LIR subgroups appears to be comparable. For the cancer trial, V9236, the secondary efficacy results also consistently showed very similar treatment effects, and, thus, are in support of the primary endpoint showing efficacy of naldemedine in both the LIR and the non-LIR subgroups.

Thus is it reasonable to conclude that naldemedine will be effective in LIR as well as non-LIR patients.

PK

The effect of moderate inducers (e.g. efavirenz) is not established; therefore, the use of naldemedine should cautiously be considered in patients already treated with a moderate inducer (see SmPC sections 4.4 and 4.5).

3.4. Unfavourable effects

Treatment with naldemedine 0.2 mg was generally well tolerated both in subjects with chronic non-cancer pain and OIC and subjects with cancer and OIC.

In all populations and subgroups, irrespective of definition, naldemedine-treated patients had an increased incidence of TEAEs belonging to the SOC of GI Disorders. This signal was primarily carried by an increased incidence of abdominal pain, diarrhoea, nausea and vomiting. These TEAEs are considered to be adequately addressed in the proposed SmPC. Bearing in mind the mechanism of action of naldemedine, it appears plausible that a causal relationship between administration of naldemedine and GI AEs exists. The GI AEs were generally of mild to moderate severity and there were no GI SAEs registered. Generally, a dose-response relationship was observed and AEs typically occurred early during the course of the study.

Important identified risks of treatment are gastrointestinal symptoms (diarrhoea, abdominal pain, nausea and vomiting) and opioid withdrawal syndrome. Potential important risks of naldemedine (safety issues

reported with other PAMORA) have been identified as gastrointestinal perforation and anti-analgesic effect due to centrally-mediated opioid receptor antagonism. These risks of treatment are considered to be adequately described in the proposed SmPC.

Based on *in vivo DDI* results observed with itraconazole (Cmax, AUC0-last, and AUC0-inf of naldemedine increase by 1.12 fold, 2.65 fold, and 2.91 fold respectively), concomitant use with strong CYP3A inhibitors should be avoided. If naldemedine is used concommitantly with moderate CYP3A inhibitors, monitoring of adverse reactions is needed. This recommendation is reflected adequately in section 4.5 of the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

Important potential risks of treatment with naldemedine include gastrointestinal perforation and anti-analgesic effect due to centrally-mediated opioid receptor antagonism. No events of gastrointestinal perforation were reported with naldemedine during the study. However, this has been observed with other peripherally acting mu-opioid receptor antagonists. Naldemedine is contraindicated in patients with known or suspected gastrointestinal obstruction or patients at increased risk of recurrent obstruction due to the potential for gastrointestinal perforation. In addition, the SmPC contains a warning regarding use in patients with GI malignancies included in the section regarding gastrointestinal perforation.

As naldemedine is a μ-receptor antagonist, it has the potential to affect centrally-mediated μ-receptor agonist activity. This potential risk is expected only to be of relevance in patients who have disruptions to the blood-brain barrier (e.g. patients with primary brain malignancies, CNS metastases or other inflammatory conditions). A warning regarding the potential for increased risk of reduced analgesia due to centrally-mediated μ-receptor antagonism is included in the SmPC.

Missing information listed in the RMP includes the following:

- Long-term use (more than 1 year) safety due to the limited duration of the registration studies.
- Use in patients with severe renal and hepatic impairment as these were excluded from the clinical studies.
- Use in children and use in pregnant or breast-feeding women as these were excluded from the clinical studies.
- Patients at high risk of cardiovascular events as these were excluded from the clinical studies.
- Patients aged 75 years and older as these were not included in sufficient numbers in the clinical studies.
- Effect of concurrent methadone use. This has not been studied independently. However, patients treated with methadone were included in the overall study population.

3.6. Effects Table

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Proportion of SBM responders	SBM responders were defined as at least 3 SBMs/week with at least 1 SBM/week increase over baseline for at least 9 out of 12 weeks and at least 3 of the last 4 weeks	%	47.6	34.6	Collection and handling of SBM data	V9231
			52.5	33.6		V9232
			50.1	34.1		Pool of V9231+ V9232
	SBM responders were defined as at least 3 SBMs/week and an increase in frequency of SBM from baseline of at least 1 SBM/week during the 2-week treatment period.	%	77.6	37.5		V9222
			71.1	34.4		V9236
			73.5	35.5		Pool of V9222+ V9236
Proportion of SBM responders - LIR subgroup	SBM responders were defined as	%	46.4	30.2	Collection and handling of SBM data Definition of the LIR subgroup not according to	Pool of V9231+ V9232

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Proportion of SBM responders - non-LIR subgroup	at least 3 SBMs/week with at least 1 SBM/week increase over baseline for at least 9 out of 12 weeks and at least 3 of the last 4 weeks	%	54.3	38.9	guideline	Pool of V9231+ V9232
Proportion of SBM responders - LIR subgroup	SBM responders were defined as at least 3 SBMs/week (on average) with at least 1 SBM/week (on average) increase over baseline at both Week 1 and 2 of the treatment period	%	57.1	32.1		V9221
Proportion of SBM responders - non-LIR subgroup			60.0	25.0		V9221
Proportion of SBM responders - LIR subgroup	SBM responders were defined as	%	61.7	25.6		Pool of V9222+ V9236

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Proportion of SBM responders - non-LIR subgroup	at least 3 SBMs/week and an increase in frequency of SBM from baseline of at least 1 SBM/week during the 2-week treatment period.		60.0	18.2		Pool of V9222+ V9236
Unfavourable Effects						
Non-cancer patients						
GI AEs	Abdominal pain	+	NAL 0.2 mg N=87 (7.1%)	Placebo N=28 (2.3%)	Difference (95% CI) 4.8 (3.2 , 6.5)	Non-cancer Phase 2b and 3
GI AEs	Diarrhoea	+	NAL 0.2 mg N=113 (9.2%)	Placebo N=49 (4.0%)	Difference (95% CI) 5.2 (3.3 , 7.2)	Non-cancer Phase 2b and 3
GI AEs	Nausea	+	NAL 0.2 mg N=79 (6.5%)	Placebo N=52 (4.2%)	Difference (95% CI) 2.2 (0.4 , 4.0)	Non-cancer Phase 2b and 3
GI AEs	Vomiting	+	NAL 0.2 mg N=45 (3.7%)	Placebo N=26 (2.1%)	Difference (95% CI) 1.6 (0.2 , 2.9)	Non-cancer Phase 2b and 3
ADR OW <12 wks	Definite reaction	+	NAL 0.2 mg N=10 (0.9%)	Placebo N=6 (0.5%)	-	Non-cancer

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Cancer patients						
GI AEs	Abdominal pain	+	NAL 0.2 mg N=5 (3.2%)	Placebo N=1 (0.7%)	Difference (95% CI) 2.6 (-0.5 , 5.6)	Cancer Phase 2 and 3
GI AEs	Diarrhoea	+	NAL 0.2 mg N=45 (29.0%)	Placebo N=24 (15.8%)	Difference (95% CI) 13.2 (4.0 , 22.4)	Cancer Phase 2 and 3
GI AEs	Nausea	+	NAL 0.2 mg N=7 (4.5%)	Placebo N=9 (5.9%)	Difference (95% CI) -1.4 (-6.4 , 3.6)	Cancer Phase 2 and 3
GI AEs	Vomiting	+	NAL 0.2 mg N=6 (3.9%)	Placebo N=2 (1.3%)	Difference (95% CI) 2.6 (-1.0 , 6.1)	Cancer Phase 2 and 3
Metabolism and nutrition AEs	Decreased appetite	+	NAL 0.2 mg N=9 (5.8%)	Placebo N=2 (1.3%)	Difference (95% CI) 4.5 (0.4 , 8.6)	Cancer Phase 2 and 3
ADR OW <12 wks	Definite reaction	+	NAL 0.2 mg N=0	Placebo N=0	-	Cancer

Abbreviations: GI: Gastrointestinal, AEs: Adverse events, wks: weeks, ADR: Adverse drug reaction, OW: Opioid withdrawal, NAL: naldemedine

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The population included in the pivotal studies represent patients with opioid induced obstipation. Naldemedine 0.2 mg vs. placebo have shown a clinical relevant increase in the number of spontaneous bowl movements in both cancer patients and non-cancer patients treated with up to 400 mg MED. Post-hoc analyses defining the clinical trial population as LIR and non-LIR patients groups have shown consistent efficacy in both groups. In addition, analyses of patients who can be considered laxative naïve have also shown naldemedine to be effective for a 12 week period. The definition of LIR and non-LIR was done post-hoc but the definition was in-line with the guideline. It was done post-hoc as the studies were conducted prior to the current guideline being published. However, it is noted that strictly laxative naïve patients (patients who never took laxatives for OIC treatment) have not been studied and laxative naive

subjects in the post hoc analyses were defined as a subject who did not use any laxatives from 90 days to 1 day before first dose, and used only rescue laxatives after first dose or did not use any laxatives after first dose). The uncertainty about the treatment effect of naldemedine in patients treated with high opioid doses has adequately been addressed in the SmPC with a statement that there is limited experience in patients treated with more than 400 mg MED.

Naldemedine has been studied in both OIC patients with adequate response to laxatives (non-LIR) and in patients with inadequate respond to laxatives (LIR). However, as mentioned strictly laxative naïve patients have not been studied and thus the indication was amended during the procedure to patients who have previously been treated with laxatives.

The presented analyses of efficacy in LIR and non-LIR patients indicated that naldemedine has statistically significant and clinically relevant efficacy across these patient groups.

The use of naldemedine is, as expected, associated with gastrointestinal adverse events, in particular abdominal pain, diarrhoea, vomiting and nausea. However, each of these events affected less than 10% of the patients and most AEs were not serious. No gastrointestinal perforations were seen with naldemedine, however this has been observed with other peripherally-acting μ-opioid receptor antagonist (PAMORAs) and could be a class effect. This is adequately addressed in the SmPC and RMP. Only very few patients had signs of opioid withdrawal indicating that naldemedine does not cross the blood brain barrier to such a degree that it causes clinically relevant symptoms. A warning to use naldemedine with caution in patients with a risk of having a compromised blood brain barrier such as patients with brain metastases is included in the SmPC.

Its safety profile in different subgroups (LIR, non-LIR, regardless of sex, BMI, type and dose of opioids) is consistent with that observed in the overall population (non-cancer and OIC population and cancer and OIC patients).

3.7.2. Balance of benefits and risks

The data presented indicate that naldemedine has a statistically and clinically significant effect in laxative experienced patients with OIC and that the safety profile is considered benign and manageable in this population.

3.8. Conclusions

The overall B/R of Rizmoic is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Rizmoic is favourable in the following indication:

Rizmoic is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have previously been treated with a laxative.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that naldemedine is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.