25 September 2014
EMA/CHMP/738815/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Moventig

International non-proprietary name: naloxegol

Procedure No. EMEA/H/C/002810/0000

Note

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

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Administrative information

Name of the medicinal product:	Moventig
Applicant:	AstraZeneca AB SE-151 85 Södertälje Sweden
Active substance:	naloxegol oxalate
International Nonproprietary Name/Common Name:	naloxegol
Pharmaco-therapeutic group (ATC Code):	Drugs for constipation (A06AH03)
Therapeutic indication(s):	Moventig is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s).
Pharmaceutical form:	Film-coated tablet
Strengths:	12.5 mg and 25 mg
Route of administration:	Oral use
Packaging:	Blister
Package sizes:	12.5 mg: 30 (3x10) tablets, 90 (9x10) tablets and 90 x 1 tablets (unit dose) 25mg: 10 (1x10) tablets, 30 (3x10) tablets, 90 (9x10) tablets and 90 x 1 tablets (unit dose)

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List of abbreviations

ADME Absorption, distribution, metabolism and excretion

ADR Adverse Drug Reaction

AE Adverse event

ALMP Abuse Liability Monitoring Plan

AUC Area under the concentration time curve

BA Bioavailability

BBB Blood-brain barrier

BCS Biopharmaceutics Classification System

BE Bioequivalence

BLRSQ Baseline Laxative Response Status Questionnaire

BMI Body mass index

BP Blood pressure

CEP Certification of suitability to the monographs of the European Pharmacopoeia

CHMP Committee for Medicinal Products for Human Use

CI Confidence interval

CL Clearance

Cmax Maximum plasma drug concentration

CMH Cochran-Mantel-Haenszel

CNS Central nervous system

CQA Critical quality attribute

CSP Clinical study protocol

CSR Clinical study report

C-SSRS Columbia-Suicide Severity Rating Scale

CYP3A4 Cytochrome P450 3A4

CV Cardiovascular

CV-EAC Cardiovascular event adjudication committee

DAE Discontinuation of investigational product due to an AE

DEA US Drug Enforcement Administration

DAMGO [D-Ala2, N-MePhe4, Gly-ol]-enkephalin

EC European Commission

ECG Electrocardiogram

eDiary Electronic diary

EDQM European Directorate for the Quality of Medicines & Healthcare

EFD Embryo-fetal development

EMA European Medicines Agency

EU European Union

FDA US Food and Drug Administration

GC Gas chromatography

GI Gastrointestinal

GI-EAC Gastrointestinal event adjudication committee

HPLC High performance liquid chromatography

ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IP Investigational Product

IPC In-process control

IR Immediate release

IR Infrared spectroscopy

ISR incurred sample reproducibility

ITT Intent-to-treat

KF Karl-Fischer titration

LAR Laxative Adequate Responder/Response

LCMS Liquid chromatograpy mass spectrometry

LIR Laxative Inadequate Responder/Response

LS Mean Least-Squares Mean

LUR Laxative Unknown Responder/Response

MACE Major adverse cardiovascular event

MedDRA Medical Dictionary for Regulatory Activities

meu Morphine equivalent units

mHS Modified Himmelsbach scale

MI Myocardial infarction

MMRM Mixed model for Repeated Measures

MTP Multiple Testing Procedure

Naloxegol Also known as NKTR-118, PEG-naloxol, NKT-10018, as naloxol 6α-

methoxyhepta(ethylene glycol) ether, also known as α-6-mPEG7-O-naloxol.

Naloxegol oxalate salt International Union of Pure and Applied Chemistry (IUPAC) name is (5a,6a)-17-allyl-6-(2,5,8,11,14,17,20-heptaoxadocosan-22-yloxy)-4,5-epoxymorphinan-3,14-diol oxalate

NMR Nuclear magnetic resonance

NRS Numeric rating scale

OCTT Oral cecal transit time

OIC Opioid induced constipation

PAC-QOL Patient Assessment of Constipation Quality of Life

PAC-SYM Patient Assessment of Constipation Symptoms questionnaire

PAMORA Peripherally acting μ-opioid receptor antagonist

PBPK Physiologically-based pharmacokinetic modeling

PCI Potentially clinically important

PDCO Paediatric Committee

PEG Polyethylene glycol

P-gp P-glycoprotein

Ph. Eur. European Pharmacopoeia

PIP Paediatric Investigation Plan

PK Pharmacokinetic(s)

PPI Proton Pump Inhibitors

PRO Patient reported outcome

PRMP Patient Risk Management Plan

PT Preferred Term

QD Every day/once daily

QoL Quality of Life

QTcF Fridericia corrected QT interval

QWBA quantitative whole body autoradiography

RH Relative humidity

SAE Serious Adverse Event

SAP Statistical analysis plan

SBM Spontaneous bowel movement

SmPC Summary of product characteristics

SMQ Standardized MedDRA Queries

SOC System Organ Class

T1/2 Half-life

Tmax Time of maximum plasma drug concentration

US United States of America

UV Ultraviolet spectroscopy

XRPD X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 26 August 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Moventig, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 October 2012.

The applicant applied for the following indication: "Moventig is indicated for the treatment of adult patients 18 years and older with opioid-induced constipation (OIC) including patients with inadequate response to laxatives."

The legal basis for this application refers to:
Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that naloxegol 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 P/0183/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0183/2012 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 naloxegol contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 22 April 2010, 21 July 2011 and 25 April 2013.

The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in Canada.

The product has been licensed in USA on 16 September 2014 under the trade name of Movantik.

1.2. Manufacturers

Manufacturers responsible for batch release

AstraZeneca AB
Gärtunavägen
SE-151 85 Södertälje
Sweden

AstraZeneca UK Limited
Silk Road Business Park
Macclesfield
Cheshire
SK10 2NA
United Kingdom

1.3. Steps taken for the assessment of the product

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

Rapporteur: Bart Van der Schueren Co-Rapporteur: Piotr Fiedor

- The application was received by the EMA on 26 August 2013.
- The procedure started on 25 September 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 December 2013 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 December 2013.
- During the meeting on 9 January 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 23 January 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 January 2014 .
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 April 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 28 May 2014 .
- During the CHMP meeting on 26 June 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant .
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 August 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of

Outstanding Issues to all CHMP members on 4 September 2014.

- During the meeting on 11 September 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan .
- During the meeting on 25 September 2014, 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 Moventig.

2. Scientific discussion

2.1. Introduction

Opioid analgesics are the mainstay in the treatment of moderate-to-severe pain (Camilleri 2011, Holzer 2007, WHO 1996); however, their use is frequently associated with adverse effects, the most common and debilitating being OIC (Holzer 2007). Opioids stimulate nonpropulsive activity, increase the constrictive tone of sphincters and decrease secretion of fluids in the gastrointestinal tract. The decrease in content propulsion results in prolonged transit time and increased contact time, increasing fluid absorption. The resulting accumulation of hard, dry stool is the basis for the OIC symptoms of constipation (Camilleri 2011, Brock et al 2012, Chou et al 2009, McNicol et al 2008, Panchal et al 2007).

OIC can significantly interfere with activities of daily living, resulting in a lower quality of life. OIC patients have a significantly greater resource use than opioid users without OIC, including increased physician visits, and alternative care visits (Bell et al 2009, Panchal et al 2007).

Existing guidelines generally agree on using prophylactic laxative as the first-line preventative treatment for OIC, initiated at the same time as opioid treatment. 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). While prescription (eg, lactulose) or over-the-counter laxatives (eg, senna and bisacodyl) are commonly used to treat OIC in clinical practice, they do not specifically target the opioid mediated mechanisms that cause constipation, and often fail to provide adequate treatment for many patients. Other available treatment options include methylnaltrexone (a subcutaneous injection for patients with advanced medical illness, available in the US, EU and Canada), and lubiprostone (approved in the US as an oral treatment of OIC in patients with chronic non cancer pain).

Patients receiving opioids for their pain have a clear unmet medical need and would benefit from an oral therapy that directly addresses the underlying OIC GI pathophysiology and that provides a durable and consistent relief. The need is especially apparent for patients who continue to have constipation symptoms despite treatment with laxatives (eg, Muller-Lissner 2013, Bell et al 2009).

The physiological effects of opioids are primarily mediated by 3 well-characterized opioid receptor sub-types, mu (μ), kappa (κ) and delta (δ) (Holzer 2007). Mu-opioid receptors are widely distributed in the central nervous system (CNS) and are involved in the perception of pain, and in the mesenteric and sub-mucosal plexi of the enteric nervous system where they regulate peristaltic activity. Thus while the analgesic effects of exogenous opioids rely upon distribution to the CNS, their interference with normal function of the gut, underlying the development of OIC, is thought to be primarily via distribution to tissues outside the blood-brain barrier (BBB) (based on Camilleri 2011).

Naloxegol is a μ-opioid receptor antagonist that has been developed as an oral treatment for OIC. In receptor binding experiments, it is a full competitive antagonist of μ-opioid receptors, an antagonist of δ-opioid receptors and a weak partial agonist at the κ-opioid receptors, with the highest binding affinity at μ-opioid receptors (27 fold more potent binding at mu than delta receptors).

Naloxegol is PEG naloxol, also known as a PEGylated derivative of naloxone. It is a substrate of the P-glycoprotein (P-gp) transporter, which substantially limits its ability to cross the BBB. Naloxegol, by binding to μ-opioid receptors within the GI tract targets the underlying causes of OIC. With its antagonist

effects essentially restricted to the opioid receptors located outside the CNS, naloxegol is expected to alleviate OIC without reducing the central analgesic effects of opioids. Naloxegol tablets are to be administered once daily, in the morning (to avoid bowel movements in the middle of the night) on an empty stomach at least 30 minutes prior to the first meal of the day or 2 hours post-meal. The recommended therapeutic dose is 25 mg. The naloxegol dose should be decreased to 12.5 mg daily when co-administered with dual P-gp/moderate CYP3A4 inhibitors.

Naloxegol has the potential to offer clinical benefits compared with existing therapies as an oral agent in the peripherally-acting mu-opioid receptor antagonist (PAMORA) class developed for patients with OIC.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 12.5 and 25 mg of naloxegol as active substance.

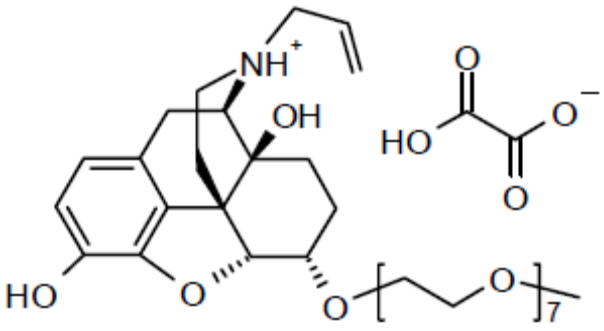
The other ingredients are mannitol (E421), microcrystalline cellulose (E460), croscarmellose sodium (E468), magnesium stearate (E470b) and propyl gallate (E310) in the tablet core and hypromellose (E464), titanium dioxide (E171), macrogol (E1521), iron oxide red (E172) and iron oxide black (E172) in the tablet coat.

The product is available in alu/alu blisters.

2.2.2. Active Substance

General information

The chemical name of naloxegol is (5α,6α)-17-allyl-6-(2,5,8,11,14,17,20-heptaoxadocosan-22-yloxy)-4,5-epoxymorphinan-3,14-diol oxalate and has the following structure:



The structure of naloxegol was unambiguously confirmed by ^{1}H and ^{13}C NMR, including 2D correlation experiments, IR spectroscopy, mass spectrometry, single crystal X-ray crystallography, and the synthetic process, taking into account the structures of starting materials, reagents, and intermediates.

The active substance is a white to off-white crystalline solid, highly soluble in aqueous media according to BCS classification, highly soluble in ethanol and very slightly soluble in isopropyl ether. Only minor

moisture uptake is observed below 70% RH, but absorption increases rapidly above this threshold at 80% RH and the compound subsequently deliquesces.

Naloxegol exhibits stereoisomerism due to the presence of 5 contiguous chiral centres. Enantiomeric purity is controlled routinely by specific optical rotation in the specification of the naloxone hydrochloride starting material which contains 4 of the stereocentres which can't epimerise in the subsequent synthetic sequence. The fifth stereocentre is installed by a diastereoselective reduction. Analytical methods have been demonstrated to detect and quantify the minor diastereoisomer which show that this impurity is controlled to an acceptable level by the process. Polymorphism has been observed for naloxegol with a second polymorphic form accessible under specific crystallisation conditions. However, this has been shown by XRPD data to be excluded under the commercial process. Given the high aqueous solubility of the active substance, the physical form of the active substance is considered to be well controlled.

Naloxegol is a chemical substance not previously authorised as a medicinal product in the European Union. Furthermore, it is not a salt, complex, derivative or isomer, (nor mixture of isomers), of a previously authorised substance. It is structurally related to the previously authorised substance Naloxone from which it is synthesized by reduction and PEGylation. However, the applicant presented data indicating that the PEG group is stable to metabolic cleavage and that Naloxegol and Naloxone do not share active metabolites. Therefore, the therapeutic moieties are not the same. Naloxegol thus meets the definition of a New Active Substance according to the Notice to Applicants (NtA), Vol 2A, Chapter 1, Annex 3.

Manufacture, characterisation and process controls

Naloxegol is synthesized in four synthetic steps from, naloxone hydrochloride dihydrate, and two other starting materials. Naloxone hydrochloride dihydrate is itself an authorised active substance and the applicant has provided valid CEPs from the proposed suppliers to justify its suitability as a starting material. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability. The proposed specifications are the same as those from Ph. Eur. with the omission of additional tests present in each individual CEP. The absence of these additional tests is well justified. The other two starting materials are well-defined materials with acceptable specifications.

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 fate and have been fully characterised. Genotoxic impurities have been discussed and appropriate limits set to limit them in the isolated active substance.

Adequate in-process controls (IPCs) are applied during the synthesis and those IPCs critical to active substance quality have been defined and explained thoroughly. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are justified based on a thorough understanding of origin, fate, and purge of impurities.

Specification

The active substance specification includes tests for appearance, identity (IR, ^{13}C NMR – also identifies counter-ion), assay (HPLC), impurities (HPLC), 2 potential genotoxic impurities (HPLC, LCMS), residual solvents (GC), and residue on ignition (Ph. Eur.). The absence of tests for water, particle size distribution and polymorphic form is considered justified. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis data for 19 batches of naloxegol and 39 batches of naloxegol oxalate, 12 of which were manufactured at production scale and using the process intended for commercial supply, have been provided. The results of the 12 commercial scale batches were well within the specifications and consistent from batch to batch.

Stability

Stability data on 6 pilot scale batches (3 using proposed commercial process, 3 using a very similar process with only a minor change in active substance crystallization process) of active substance from the proposed manufacturer, stored in the intended commercial package for up to 18 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. All parameters with the potential to change on stability were studied. The parameters tested were the same as for release with the absence of tests for identification, 1 potential genotoxin and sulfated ash. Additional tests for known degradants, water content, polymorphic form and microbiological quality were included. There was no significant change to any of the tested parameters under either storage condition.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. Stressed studies were carried out on 1 batch at 50 ^{o}C for 1 month and a further batch open to the atmosphere for 4 weeks. The parameters tested and the methods used were the same as for primary stability batches with the omission of tests for polymorphic form and microbiological quality. There was no significant change to any of the tested parameters under all the storage conditions, indicating excellent stability of the active substance.

Forced degradation was carried out under acidic (pH1), neutral (pH7) and alkaline (pH13) aqueous conditions in sealed containers in either light or dark and stored at ambient temperature or in a refrigerator for 7 days, or under oxidative conditions (0.3% H_2O_2). No major degradation was observed, although several relevant degradation products were identified. The results demonstrate that the analytical methods are stability indicating.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 30 months in the proposed container.

The applicant commits to the continuation of all on-going stability studies under long term conditions up to the 48 month time point. In addition, stability studies will be carried out on 3 early commercial batches of naloxegol under long term, intermediate, and accelerated conditions. Furthermore, at least 1 commercial batch per year will be placed on a long-term stability study.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The objective of formulation development was to develop immediate-release oral dosage forms of naloxegol in two strengths, with reliable release and bioavailability characteristics and adequate quality over the product shelf-life. The active substance is a chemically stable crystalline solid, routinely manufactured as a single stable polymorph. It is highly soluble in aqueous media from pH1-7.5 but has

low intestinal permeability (BCS class III). The finished product shows fast dissolution over the range of active substance particle sizes tested. The content uniformity of tablet cores was also consistent when manufactured from active substance batches with varying particle size distribution. Therefore, particle size distribution is not considered critical and no limit is set for the active substance.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. Their compatibility with the active substance was demonstrated by long-term and accelerated stability studies. A post-authorisation change management protocol has been approved to allow modifications to the process for modifying and controlling propyl gallate particle size distribution. The compositions of the 2 tablet strengths are proportional.

Dry processing techniques were used throughout development. Critical quality attributes (CQAs) for the finished product were defined as tablet description, active substance identification, assay, degradation products, dissolution, uniformity of dosage units, water content and microbiological quality. These CQAs directed a series of development studies looking at levels of different excipients optimising compaction, disintegration and dissolution time with the tablets' mechanical properties, as well as preventing degradation and ensuring uniformity and robustness of formulation to minor variations in excipient and active substance quality. The film-coating is added to produce uniform tablets meeting the appearance CQAs and does not affect the dissolution profile.

A loss in crystallinity is observed for the active substance once formulated and this is due to interaction with water in intra-tablet micro-environments and the deliquescent nature of the active substance at high relative humidity. No increase in degradation is observed, nor is there any significant change to the dissolution properties, and thus, no tests for drug substance crystallinity are required.

The discriminatory power of the dissolution method has not been demonstrated. However, development studies have consistently demonstrated that dissolution is always rapid, independent of critical manufacturing parameters, and so a discriminatory test is not considered to be important for the finished product.

The original formulations used in clinical trials (phases I-III) employed naloxegol free base which is a hygroscopic, water-soluble oil, sensitive to degradation on exposure to heat, light, or oxidants, and thus requiring special handling, shipping, and storage conditions. The phase I formulation was an aqueous solution whereas later studies employed film-coated tablets containing naloxegol free base. An *in vivo* study demonstrated that the free base aqueous solution and the oxalate salt immediate release tablet are bioequivalent. The crystalline oxalate salt was selected for the commercial formulation because it is much more stable which allows for simpler handling and storage. *In vivo* bioequivalence to the phase III free base formulation was demonstrated for the commercial 25 mg film-coated tablet. A biowaiver for the 12.5 mg commercial film-coated tablet was accepted because it is has the same dose-proportional composition as the 25 mg tablet and has similar, rapid *in vitro* dissolution performance.

The primary packaging is alu/alu blisters which are available in two configurations depending on the intended user. The first is for hospital use and contains perforated blisters. The second is for all other users and is non-perforated. 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 manufacturing process consists of three main steps: 1) the active substance and excipients are blended by dry-mixing; 2) the dry blend is compressed to form tablet cores; 3) the cores are film-coated before packaging. The process is considered to be a standard manufacturing process. Therefore, formal validation of the process in the production facilities has not yet been completed but will be carried out prior to release of Moventig film-coated tablets to the market. A process validation scheme has been presented which is considered acceptable. Routine batch manufacture at the commercial manufacturing site throughout the product lifecycle will be monitored using a continued process verification approach.

In-process controls (IPCs) are carried out after the compression and film-coating steps to ensure that CQAs of the product are met. These are considered adequate to control the production of Moventig film-coated tablets. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications comprise appropriate tests for this kind of dosage form including description (visual inspection), identification (HPLC and UV), assay (HPLC), degradants (HPLC), dissolution (Ph. Eur.), uniformity of dosage unit (HPLC), water content (KF) and microbiological quality (Ph. Eur.). There are also tests for identification and assay of the propyl gallate (HPLC).

Batch analysis results are provided for 19 batches of Moventig, 7 using naloxegol free base, (which are considered as supportive data) and 12 using naloxegol oxalate, used for clinical and stability studies. Of the 12 batches made with the oxalate salt, 2 used the intended commercial process and the other 10 synthesized using a slightly different crystallization process.

All batches complied with the proposed specification, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on 3 commercial scale batches of finished product of each strength stored in the proposed commercial pack under long term conditions (25 ºC / 60% RH) for up to 12 months, under intermediate conditions (30 ºC, 75% RH) for up to 12 months, and under accelerated conditions (40 ºC / 75% RH) for up to 6 months according to the ICH guidelines were provided. These were all manufactured with active substance synthesized using a slightly different crystallization process. Samples were tested for description, assay, degradants, a potential genotoxic impurity, dissolution, water content and microbiological quality. The analytical procedures used are stability indicating. An additional two batches of tablets of each strength containing active substance manufactured by the commercial process have also been put on stability studies under long-term, intermediate and accelerated conditions although those stored under long-term conditions will only be tested if significant changes are observed under intermediate conditions. Up to 6 months of stability data is available for these batches. Analogous data has also been provided on the same 10 batches stored in a bulk pack. Little or no change was observed in either the commercial or bulk pack except for minor decrease in assay under all conditions and slight increase in degradants and associated decrease in assay under accelerated conditions.

In addition, stressed stability studies were carried out on 1 commercial scale batch of each strength. The finished product was exposed for up to 12 weeks to open conditions, for up to 3 months at 50 ºC exposed to atmospheric humidity, and for up to 1 month to light as defined in the ICH Guideline on Photostability

Testing of New Drug Substances and Products. A minor decrease in assay and increase in one degradation product was observed in both commercial and bulk pack under thermal stress. Degradation to the same degradation product was also noted in the open storage samples, along with an initial increase in water content. The photostability samples showed little or no change – other than a minor increase in 1 degradant.

Based on available stability data, the shelf-life as stated in the SmPC is acceptable.

Adventitious agents

None of the excipients used in Moventig finished product are of animal or human origin. The magnesium stearate is from a vegetable source.

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 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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical profile of naloxegol was established in a comprehensive investigational program that included studies of in vitro and in vivo pharmacology, safety pharmacology, pharmacokinetics, and toxicity.

This included a series of in vitro assays to characterize the primary pharmacological action on opioid receptors such as assays to determine binding affinities as well as assays designed to establish any agonist/antagonist activity. A battery of in vivo studies was also performed to determine the functional effect of naloxegol on central and peripheral opioid agonist-induced effects. The secondary pharmacology assessment of naloxegol was based on testing in a diverse panel of 327 targets covering a broad spectrum of receptors, ion channels and enzymes.

Naloxegol was also examined in a series of in vitro and in vivo safety pharmacology studies to assess potential effects on the central nervous, cardiovascular, gastro intestinal, respiratory, and renal systems.

All pharmacology and safety pharmacology studies were conducted with naloxegol free base. Drug interaction studies were not conducted in nonclinical animal models.

The pharmacokinetic and absorption, distribution, metabolism and excretion (ADME) properties of naloxegol have been studied in vitro and in vivo in mouse, rat, dog and monkey using the strains involved in the safety evaluation where appropriate. All studies were conducted with naloxegol free base unless identified as using the oxalate salt. Toxicokinetic monitoring of safety studies has been performed in accordance with Good Laboratory Practice using validated high performance liquid chromatography-tandem mass spectrometry detection (LC-MS/MS) methods.

A comprehensive battery of nonclinical toxicity studies was conducted to evaluate the safety profile of naloxegol. Single- and repeat-dose oral toxicity studies were conducted in mice, rats, and dogs. Recovery from drug-induced effects was evaluated in rat and dog studies.

A standard battery of in vitro and in vivo genetic toxicology studies and 2-year carcinogenicity studies in mice and rats were conducted to determine the genotoxic and carcinogenic potential of naloxegol.

A fertility study in rats, embryo-fetal development studies in rats and rabbits, and pre- and postnatal development studies in rats were conducted to determine the potential naloxegol-related effects on reproductive function, embryo-fetal development, gestation, parturition, lactation, and offspring viability and development. Additional investigative studies were conducted to explore potential mechanisms of action underlying an increased incidence of Leydig cell tumors and hyperplasia in the rat 2 year carcinogenicity study.

All toxicology studies were conducted with naloxegol free base unless identified as using the oxalate salt. Dose selection for pivotal studies was principally based on dose range finding studies or results from preceding studies to ensure that adequately high doses were evaluated.

The range of non-clinical data presented in the dossier covers reports from all main studies required for a new active substance and literature sources not designed specifically for the applicable product. The data is the basis for the discussion of this assessment report.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The primary pharmacological action of naloxegol was assessed in a number of in vitro and in vivo assays including: competitive inhibition studies performed in CHO cells expressing cloned human opioid receptors, use of membrane preparations of cells expressing cloned human μ- and δ- opioid receptors and cloned rat κ-opioid receptors and [^{35}S]GTPγS binding assay performed on membranes of Human Embryonic Kidney 293 (HEK-293S) cell. Naloxegol was further characterized for its competitive antagonism on human μ-opioid receptors in Schild-type experiments for its ability to elicit right-shifts in the concentration response curve of morphine in [35S]GTPγS binding experiments. The activity of naloxegol at δ- and κ-opioid receptors was assessed using [35S]GTPγS functional assays in CHO and HEK-293 cells, respectively

In vitro primary pharmacology data show that naloxegol is a pure antagonist at the μ-opioid receptor, as well as a δ-opioid receptor antagonist and a partial agonist at the κ-opioid receptor. Naloxegol did not display any kappa agonist activity in the isolated rabbit vas deferens tissue assay.

Naloxegol was approximately 3-fold more potent than methylnaltrexone at human μ-opioid receptors both in binding affinity and functional antagonism. At cloned human δ-opioid receptors, naloxegol was

approximately 9-fold more potent than methylnaltrexone. At cloned rat κ -opioid receptors, the binding affinity of naloxegol and methylnaltrexone were similar.

The *in vivo* data, obtained in a Rat Model of morphine-induced reversal of opioid effects, showed that naloxegol is approximately a 49-fold less potent opioid receptor antagonist than naloxone within the CNS on reversal of iv morphine analgesia. On the other hand, naloxegol can completely antagonize the effect of iv morphine on the GI tract with a potency about 33- fold less than that of naloxone. This supports that compared to naloxone, naloxegol can reverse morphine-induced slowing of GI transit at doses that do not reverse morphine analgesia.

Secondary pharmacodynamic studies

The secondary pharmacodynamics of naloxegol were assessed using a diverse panel of 327 targets covering a broad spectrum of receptors, transporters, ion channels and enzymes. Naloxegol was inactive in this panel with an exposure multiple of at least 81x the human Cmax exposure at the Maximum Recommended Human Dose (MRHD) of 25 mg (81 ng/mL). Significant activity was noted at the μ-, δ-, and κ-opioid receptors only.

Safety pharmacology programme

Naloxegol was tested in a battery of safety pharmacology studies which examined potential effects of oral naloxegol administration on the central nervous, cardiovascular, respiratory, gastrointestinal and renal systems.

A modified Irwin's screen in SD rats shows that naloxegol up to 1000 mg/kg had no effect on condition and behaviour up to 4 hours post-dose. In addition, naloxegol had no proconvulsive or analgesic activity at doses up to 1000 mg/kg in a rat PTZ model and a mouse grid stimulation analgesia model, respectively. Naloxegol had no effect in assays investigating the abuse potential. These consisted of drug-discrimination, self-administration and drug dependence studies, in which morphine was used as a positive control. Taken together, these data do not indicate that naloxegol would cause any CNS-mediated adverse events at the MRHD. When co-administered with morphine, doses of 30 mg/kg naloxegol and above antagonized the psychoactive effects of morphine, but these doses are estimated to correspond to exposures of at least 15x the human Cmax exposure at the MRHD of 25 mg (81 ng/mL). With respect to cardiovascular safety, naloxegol had an IC50 >300 μM at the hERG ion channel and was inactive against a further 7 cardiac channels. Naloxegol was inactive in a cardiac myocyte contractility assay and rat isolated heart model. However, in a conscious dog telemetry study, administration of doses of naloxegol above 5 mg/kg was associated with moderate, reversible and non dose-related decreases from baseline in arterial blood pressure (-9%), left ventricular systolic pressure (-13%) and indices of cardiac contractility. The NOEL corresponded to a measured Cmax value of 99 ng/mL, and hence approximately equal to the human exposure at the MRHD (81 ng/mL). However, ECG and blood pressure were also measured as part of the dog toxicology studies (14-day, 28-day and 9-month) and no treatment-related effects on these parameters were noted in any of these studies. In addition, in the clinical safety data, similar findings have not been reported. In conclusion, the observed effects in the dog telemetry study are probably of low relevance for humans at the intended therapeutic doses.

Rat plethysmography, gastric emptying/intestinal transport and renal function studies indicated that naloxegol is unlikely to have any adverse effect on the respiratory system, gastrointestinal or renal systems at the MRHD. At higher doses, naloxegol increased stomach weight and inhibited intestinal transport. The NOELs for these effects corresponded to 15x and 112x the exposures at the MRHD, respectively.

Pharmacodynamic drug interactions

With the exception of studies which assessed the effect of naloxegol on morphine induced parameters listed above, no studies investigating pharmacodynamic drug interactions were conducted.

2.3.3. Pharmacokinetics

The pharmacokinetic properties of naloxegol have been studied in vitro, and in vivo using the species and strains involved in the safety evaluation. All studies were conducted with naloxegol free base unless identified as using the oxalate salt. Analytical methods for naloxegol, naloxegol glucuronide and naloxone were developed by Nektar Therapeutics and used by them and at Contract Research Organisations to support the development of naloxegol. Toxicokinetic monitoring of safety studies has been performed in accordance with Good Laboratory Practice using validated high performance liquid chromatography-tandem mass spectrometry detection methods. The assays have been applied to plasma and urine samples from mouse, rabbit, dog, and monkey and to plasma, urine and bile from rat.

An in vitro study in Caco2 cells and an in situ permeability study at low doses in rats indicate that the PEG chain in naloxegol results in lower intrinsic permeability across membranes as compared to naloxone and suggest that naloxegol is a Pgp substrate, which corresponds to the intended pharmacokinetic properties.

Bioavailability after a single oral dose is low in dogs and monkeys. Data in rat or mouse are not presented. It is not possible to compare the bioavailability in animals with corresponding human data since the absolute oral bioavailability in humans has not been determined.

Steady state AUC data from the toxicology studies indicate that the exposures in animals were significantly greater than the human exposure at the MRHD of 25 mg (330 ng.h/mL). The exposure increased with dose in all species and was sometimes more than proportional at high doses. Exposure was higher in male mice and female rats but there was no sex difference in dogs. The exposure of mice is lower than in other species, particularly at high doses.

The exposure in rats in terms of Cmax and AUC are reported to be similar after administration of naloxegol as free base or oxalate salt.

The plasma protein binding of naloxegol was low in all species that were tested (mouse 14.1%, rat 20.8%, monkey, 9.7% and human 4.2%; in dogs it was concentration dependent with a maximum of around 50%). Hence, exposure margins have been calculated using total concentrations. There are no data on protein binding in rabbits.

Naloxegol mainly distributes in the liver, kidney, small intestine wall, glandular tissues (pituitary, preputial gland), reproductive organs (uterus, placenta) and pigmented tissues (uveal tract). A sex difference was observed for the female rats, i.e. an earlier Tmax and higher concentrations than males. This is in line with the TK data for rat and is attributed to the sex linked expression of the major metabolic enzymes involved. Significantly less and slower brain penetration compared to naloxone was confirmed in an in vivo brain penetration study.

Naloxegol is excreted in rat milk, it remains unknown whether in addition to naloxegol itself the metabolites are also excreted in rat milk.

The major metabolic processes of naloxegol in humans are N-dealkylation and oxidative metabolism of the PEG chain, including partial cleavage but not complete removal of the chain. Glucuronide conjugation at the phenol hydroxyl is also a common process in animals and man but the naloxegol glucuronide shows very low concentrations in the human plasma. Four significant circulating metabolites were identified (M1, M7, M10 and M13) in humans, mice, rats and dogs and the major metabolizing enzymes involved in man seem to be CYP3A4/5.

There is no metabolite in human plasma or urine that exceeds 10% of the parent drug. In addition, no metabolites unique to humans were identified after metabolite comparison across species. The similarity of the metabolic process observed across species supports the use of the mouse, the rat and the dog for the toxicological testing. Apart from the TK data for naloxegol and naloxegol-glucuronide, there are no data on the metabolism in rabbits.

Excretion is mainly fecal in all species, with renal excretion to a lesser extent. In male rats the excretion is predominantly biliary.

Data from in vitro drug interaction experiments have demonstrated that naloxegol is a Pgp substrate but is not a direct inhibitor of CYP enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4) nor transporters (Pgp, BCRP, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3) at expected concentrations in humans. As a Pgp substrate, naloxegol absorption and its distribution into the brain could be increased if coadministered with Pgp inhibitors. Since it is predominantly metabolised by CYP 3A4/5, inducers or inhibitors of these enzymes would be expected to affect the naloxegol concentration. Both interactions have been investigated and confirmed through clinical studies. It is acknowledged that interaction with potent Pgp inhibitors at the blood-brain barrier, are unlikely to have a clinical impact.

2.3.4. Toxicology

The toxicity of naloxegol was adequately evaluated in mice, rats, rabbits and dogs in a comprehensive battery of GLP compliant non-clinical toxicity studies and at exposures markedly higher than the human exposures at the recommended human dose.

Single dose toxicity

Single dose oral and intravenous toxicity studies were carried out in the mouse and rat with doses up 2000 mg/kg. These studies were generally designed to identify doses for the repeat dose toxicology studies. A single dose pharmacokinetic study in dogs involved single oral doses up to 20 mg/kg, and the results are relevant to assessing the potential for adverse clinical signs up to that dose in dogs.

In mice in-life observations of intolerability (eg, decreased motor activity, hunched posture and piloerection) were seen at 2000 mg/kg. No clinical signs were observed at the other dose levels of 500 and 1000 mg/kg.

In rats naloxegol was tolerated at up to 2000 mg/kg, although slight in-life observations (eg, half-shut eyes, piloerection) were observed in some animals at doses of 500 mg/kg and above.

In the dog naloxegol was well tolerated (with the exception of sporadic soft feces) although doses in these acute pharmacokinetic studies did not exceed 20 mg/kg.

Repeat dose toxicity

Repeat dose oral toxicity studies were carried out in the mice (up to 3 months), rats (up to 6 months), and dogs (up to 9 months). A recovery period was included in the 1-month studies and the 6/9-months studies to investigate the reversibility of any toxicological finding. A 7-day study in rats and two 14-day studies in dogs served as dose-finding studies for the 1- and the 3-months studies. The 3-months studies in rats and mice served as dose-finding studies for the 2-year carcinogenicity studies.
Most of the effects observed in the pivotal repeat-dose toxicity studies in the two main toxicology species, the rat and dog, and the mouse as a second rodent species for carcinogenicity assessment, were generally limited to effects on body weight and food consumption as well as stress-related findings which occurred at dose levels above the NOAEL and generally at doses at or close to the maximum tolerated dose level. The assessment of effects on the gastrointestinal system in an acute safety pharmacology

study demonstrated a naloxegol-mediated increase in stomach weight and inhibition of intestinal transport at ≥100 mg/kg and this effect on the GI tract could at least in part explain the decreases in body weight gain and food intake observed in the repeat dose toxicity studies.
Whilst most findings in the repeat dose toxicity studies were likely not related to inhibition of opioid receptor signaling, a dose-related finding of soft stool/diarrhoea in the dog may reflect exaggerated pharmacological effects. Some findings, such as ataxia, tremors and hypoactive behavior seen at high doses in the dog, were likely to be indicative of CNS exposure. This is not considered to be relevant for naloxegol at the intended clinical dose.
The observed neoplasms in the 3 month and 6 month rat studies do not show a dose-relationship, the tumors were of different origin, there were no increases in pre-neoplastic lesions in other animals of the same study or in the other rat studies and similar lesions were not reproduced in the 2-year carcinogenicity studies. Therefore these findings are not considered to be of concern at the proposed human dose.
The target organ of toxicity identified across all main toxicity species was the liver (weight increase and associated hypertrophy in rats, weight increase in dogs), but these findings were slight, adaptive and reversible. These findings occurred at exposures sufficiently above the maximum human exposure and are hence to be considered of little relevance to clinical use. In addition, clinical safety data do not indicate that administration of naloxegol has adverse effects on the human liver (no effects on cholesterol, AST, ALT levels).
Non-clinical exposure multiples at the NOAEL for any other findings in the chronic toxicity studies were at least 248x (rat 6-month chronic toxicity study) and greater than 35x (dog 1-month toxicity study) the human exposure at the MRHD.

Genotoxicity
Naloxegol free base was evaluated in the standard genetic toxicology battery, including the bacterial mutation (Ames) test, the mouse lymphoma TK assay and the mouse bone marrow micronucleus test. Naloxegol free base was found to be positive in the Ames test. Naloxegol free base was negative in the mouse lymphoma TK assay and the in vivo micronucleus assay. Naloxone has also been shown positive in the Ames mutagenicity and in vitro human lymphocyte chromosome aberration tests but was also not genotoxic in vivo. In addition, phenanthrene-based drugs, to which naloxegol and naloxone belong, as a class do not seem to represent a carcinogenic risk to patients (Aardema et al, 2008). However, following the identification of glycidaldehyde as a genotoxic degradation product in various batches of naloxegol free base, naloxegol oxalate was selected for commercial formulation which avoids the formation of this genotoxic degradation product. Naloxegol oxalate was negative in the Ames test. The amount of glycidaldehyde that is still present as impurity has been measured to be below 10 ppm and is thus present in amounts below the TTC, which is acceptable.

Carcinogenicity
Naloxegol was tested in rodent carcinogenicity studies in CD1 mice and Sprague-Dawley rats. The carcinogenic potential of naloxegol when administered daily via oral gavage to mice and rats was evaluated in carcinogenicity studies of approximately 2 years in duration
There were no naloxegol-mediated neoplastic changes in the mouse carcinogenicity study but an increase in Leydig cell hyperplasia and adenoma was seen in males in the rat carcinogenicity study. Leydig cell tumours are a common testicular tumour type in rodent carcinogenicity studies, especially in Fisher 344 rats. However, the incidence in Sprague-Dawley rats is usually less than 5%. Similar tumours or pre-neoplastic lesions were not seen in the 6-month rat study.
Investigative work identified the underlying mechanism as a hormonal- and centrally mediated opioid antagonistic effect involving a naloxegol-mediated increase in luteinizing hormone. The suggested mode of action is already described for other drugs that are reported to produce Leydig cell tumours in rodents.

Many of these are non-genotoxic and appear to modify pathways that regulate the hypothalamic - pituitary- gonadal axis, often ultimately producing elevations in serum luteinizing hormone and consequent Leydig cell response. In most instances, the modifications of the hormonal control mechanisms at high doses in rats are not directly relevant to humans when given these agents at therapeutic doses. Moreover, the available evidence suggests that the proliferative response of the Leydig cell in human to alterations in hormone status is far less that in the rat.
Based on the available evidence about the suggested mode of action and the non-clinical data for naloxegol, a non-genotoxic, threshold mechanism can be assumed. The exposure at the neoplastic NOAEL was 51x the human exposure at the MRHD. It is therefore expected that therapeutic naloxegol doses do not significantly increase LH levels and thus is considered unlikely that similar (pre-) neoplastic lesions in the testes of patients will be induced following chronic treatment with naloxegol.

Reproduction Toxicity

The reproductive and development toxicity studies performed include a male and female fertility study in the rat, embryo-fetal development and associated dose-range finding studies in the rat and rabbit, and a dose-range findings study for the pre- and post-natal development study as well as the actual pre- and post-natal development study in the rat.
Naloxegol did not impair fertility in rats. An increase in testis weight was observed at the highest dose group. In absence of associated histopathological changes or fertility effects and given the fact that, in the repeat-dose toxicity studies, no effects on testis weight were seen (at doses up to 500-800 mg/kg/day), this high-dose finding is not considered to be relevant for humans.
Naloxegol administration to pregnant rats resulted at the highest doses in a skeletal variation (bipartite vertebral centrum) and a visceral malformation (anorchism). Although a slight increase in the skeletal variation - within the historical control ranges - was seen at the low and mid dose, this effect was only significant at the high dose in the presence of maternal toxicity.
Naloxegol administration to pregnant rabbits resulted at the highest doses in a fetal skeletal malformation (fused arches). This effect was seen in the absence of significant maternal toxicity.
A relation to treatment cannot be excluded the effects on embryofetal development at the high doses in both rats and rabbits. However these effects were observed at exposures considered sufficiently in excess of the maximum human exposure. The exposures at the NOAEL for embryo-fetal toxicity or malformations were 1452x the human exposure at the MRHD in the rat and 79x for malformations in the rabbit. Hence, the relevance of the developmental effects observed in the rat and rabbit to human safety is considered low.
In a pre- and postnatal study in rats, a lower body weight in F1 males was evident from birth to PND 21 in all dosed groups. This effect was statistically significant in the mid and high dose (>10% decrease) and appears to be dose-related. F1 females show a similar trend during pre-weaning but fully recover post-weaning, while males don't. Therefore, the NOAEL for the F1 generation is considered to be 50 mg/kg/day, and not 500 mg/kg/day as proposed by the applicant. Although the effects are considered to be treatment-related, it is acknowledged that the clinical relevance of this finding is low in view of the high safety margin compared to the human exposure at the MRHD (maternal AUC at 50 mg/kg/day = 23291 ng*h/mL, safety margin of 70) and the absence of any other adverse effects on postnatal development.

Toxicokinetic data

The toxicokinetic data and pharmacokinetic parameters obtained in naloxegol's non-clinical studies and their comparison with respective human data indicate that the relationship between animal exposure for naloxegol associated with toxic effects was far from human exposure expected with maximum proposed dosage for applicable product.

Local Tolerance

Local tolerance studies have not been conducted. Since the proposed, clinical route of administration of applicable product is oral, there is no need for special assessment of the local tolerance of naloxegol. The lack of local tolerance studies is justified.

Other toxicity studies

Non-clinical photoreactivity or photosafety tests have not been conducted. In pigmented tissues radioactivity persisted up to 504 hours and uveal tract radioactivity concentrations were high, which indicates an association with melanin. Naloxegol oxalate shows modest absorption in the 290-700 nm range. The maximum absorption is 290 nm (UVC) with the tail extending up to 300 nm (UVB). No absorption is found in the UVA range (≥315nM). The molar extinction coefficient (MEC) of 1216 Lmol-1cm-1 at 290 nm is slightly above the threshold of 1000 Lmol-1cm-1.
The key chemical building blocks of naloxegol, principally naloxone and PEG have not been reported as presenting any photosafety risk. In addition, the clinical photosafety assessment of naloxegol based on the clinical studies conducted, supports the conclusion that naloxegol does not pose a photosafety risk in clinical use. Therefore, it is agreed that the overall photosafety risk for naloxegol oxalate is probably low and therefore further non-clinical testing is not considered necessary.

The impurities MsO-PEG4-naloxol, glycidaldehyde, α-chloro, and mPEG7-OMs were identified as mutagenic and specification of less than 400 ppm is proposed by the applicant. This threshold calculated based on a LTL (less than lifetime exposure) approach is acceptable.

2.3.5. Ecotoxicity / environmental risk assessment

Table 1. Summary of main study results

Naloxegol oxalate					
CAS-number: 1354744-91-4					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	Shake Flask Method OECD107	pH 5 log Dow < -0.326 pH 7 log Dow = -0.643 pH 9 log Dow = 0.874			Potential PBT: no
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)	0.13	µg/L			> 0.01 threshold: Yes
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Hydrolysis	OECD 111	<10% at 120 hours (pH 5, 7 and 9)			Hydrolytically stable
Adsorption-Desorption	OPPTS Guideline 835.1110	Kd sludge(ads) = 253 L/kg			Below trigger for Tier B assessment of terrestrial compartment
Ready Biodegradability Test	OECD 301B	0.7% mineralisation			Not readily biodegradable
Aerobic Transformation in Aquatic Sediment systems	OECD 308 one sediment with high (HOM) and one with low organic matter content (LOM)	DT50, water(HOM)=3.8 days DT50, water (LOM)=2.6 days DT50, whole system: could not be calculated But 50% dissipation in 7 days (HOM) and in 92 days (LOM) Highest Kd value = 120 (HOM)			No persistent breakdown products were observed
Multimatrix adsorption study	N/A	Mean Kd(ads) • Soil (in presence of 0.01M CaCl2 solution) = 19.5 • High organic sediment and natural water = 1039 • Low organic sediment and natural water = 118 • Post digester sludge and phosphate buffer = 93			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Pseudokirchneriella subcapitata* (green algae)	OECD 201	NOEC 48h	38	mg/L	NOEC based on growth rate and yield, 48h EC_{50} = 120 mg/L
Daphnia sp. Reproduction Test	OECD 211	NOEC	32	mg/	NOEC based on

(Daphnia Magna)		21day		L	reproduction and length, LOEC = 100 mg/L
Fish, Early Life Stage Toxicity Test/*Pimephales promelas* (Fathead minnow)	OECD 210	NOEC 32 day	2.0	mg/L	NOEC based on hatch, survival, length and dry weight, LOEC > 2.0 mg/L
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50} 3h	>100	mg/L	
Phase IIb Studies					
Sediment dwelling organism *(Chironomus riparius)*	OECD 218	NOEC 28 day	10	mg/kg dry sediment	LOEC > 10 mg/kg

A default PECsurface water of 0.13 µg/L has been calculated, which is above the threshold for conducting a Phase II assessment. The results of toxicity tests with microorganisms, algae, Daphnia and fish were used to calculate PNECs. The PEC/PNEC ratios for surface water and ground water are well below 1 and the PEC/PNEC for microorganisms is well below 0.1, hence no further evaluation is needed in Tier B.

Based on the adsorption coefficient to sludge, a risk assessment in the terrestrial compartment is not required. The degradation study of naloxegol in aquatic sediment systems indicates that naloxegol is rapidly shifted from water to sediment and is likely to become irreversibly bound to sediment. Consequently, the effects on the sediment dwelling organism Chironomus riparius have been investigated in Tier B. The PEC/PNEC ratio for sediment dwelling organisms was below 1. Naloxegol is not considered as PBT nor vPvB.

Considering the above data, Naloxegol is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacological profile of naloxegol is well defined. Its mode of action is typical for the class of opioid antagonists. It exhibits potent opioid antagonist activity with potential of clinical utility as proposed for applicable tablets of 12.5 mg and 25 mg. Results of in vitro and in vivo pharmacodynamic studies revealed potent action of naloxegol in terms of reversing occupation of opioid receptors (mainly µ-receptors) by opioid agonists. Non-clinical data available on naloxegol indicates that this compound exhibit similar qualitative efficacy profile compared to previously approved oral opioid antagonists for OIC.

Taking into account a common clinical practice of OIC therapy, strictly related to the two drugs interaction (opioid analgesic with agonist activity and opioid antagonist used for reversal of OIBD), it is most important to find adequate data on pharmacodynamic interactions between naloxegol and opioid analgesics. This interaction both at the peripheral level, with confirmed antagonism as expected, and CNS level, with no significant antagonism, was shown.

The knowledge about oral naloxegol pharmacokinetics, collected on the basis of submitted dossier indicates that the pharmacokinetic profiles of both naloxegol and its metabolites have been adequately examined. The collected data is sufficient for the assessment of product planned for oral administration. Based on the results of non-clinical pharmacokinetic studies it can be claimed, that due to reduced

systemic availability and low CNS permeability of naloxegol administered orally, the risk related to its CNS unwanted activity antagonizing analgesic effects of opioids in proposed clinical dosage is apparently reduced. This risk does not seem to be greater than the risk related to use of previously approved oral opioid antagonists for OIC.
There is no evidence for any basic difference in metabolic pathways of naloxegol between animals and humans. Thus, toxicological studies performed in chosen species and routes of administration are adequate for non-clinical assessment.
Naloxegol has potential for pharmacokinetic interactions with drugs related to CYP3A4/5 inhibition and/or activation. Since it is predominantly metabolised by CYP 3A4/5, inducers or inhibitors of these enzymes would be expected to affect the naloxegol concentration. Furthermore, it is acknowledged that interaction with potent Pgp inhibitors at the blood-brain barrier, are unlikely to have a clinical impact

The single-dose toxicity studies demonstrated low toxicity of naloxegol both in mice, rats and dogs.

Similarly to single dose studies, naloxegol had a low toxicity in repeat dose studies with broad margin between the exposition related to NOAEL/NOEL and exposition in humans after maximum recommended clinical dose of 25 mg/day. There was no clear evidence that there is a specific target for naloxegol toxicity.

The results of submitted genotoxicity tests did not reveal any significant risk carried by naloxegol oxalate. There was no evidence of treatment-related increases in tumor incidence following administration of naloxegol to mice. No risk to humans was found according to analysis of the mixed results of rat carcinogenicity studies.

Naloxegol has a very high safety margin for reproductive toxicity comparing to human exposition after maximum recommended clinical dose.

The impurities of naloxegol present no safety concerns for clinical practice based on the specification of less than 400 ppm as proposed by the applicant.

The environmental risk assessment of naloxegol indicate that it is assumed to pose no risk to the environment

2.3.7. Conclusion on the non-clinical aspects

The Non-clinical aspects of development for Moventig have been adequately addressed. Toxicology studies indicate a good tolerability of the product taking into consideration that toxic effects are shown in animals when in-vivo exposition is far from the exposition expected with the maximum proposed dosage in human. From a non-clinical point of view, the profile of this product is acceptable.

2.4. Clinical aspects

2.4.1. Introduction

During development of the Phase III program, there were no established treatment guidelines or generally accepted publications on diagnostic or treatment practices for patients with OIC. Therefore, the design for the studies in the naloxegol Phase III program was defined based on:

1) key scientific literature on treatment trials of OIC and chronic constipation,
2) regional treatment guidelines in the US and Europe,

3) available regulatory meeting documentation concerning other development programs for orally administered agents intended for the treatment of opioid-related bowel conditions or chronic constipation, and

4) consultation with internal and external disease experts, including the Principal Investigators.

Scientific advice was sought from the Committee for Medicinal Products for Human Use (CHMP) on the studies included in the Phase III program and the following main considerations were discussed and endorsed:

- A responder to study drug during weeks 1 to 12 was defined as a patient with at least 3 SBMs/week and at least a 1 SBM/week increase over baseline for at least 9 out of the 12 treatment weeks and 3 out of the last 4 treatment weeks during the double-blind treatment period. Thus, the primary endpoint incorporates both the durability of effect and a clinically relevant increase in the SBM rates across the 12-week treatment period.

  The original 4-week primary endpoint in the confirmatory studies was changed in a protocol amendment approximately 11 months before unblinding to response evaluated over the entire 12-week study duration. This agreement also included using a multiple testing procedure (MTP) to control the overall type-I error across the primary and key secondary endpoints, for comparisons between the 2 naloxegol doses with placebo.

- Extrapolation of US data to EU population.

A paediatric investigation plan was adopted by the PDCO in August 2012. A deferral was agreed regarding the initiation and completion of the naloxegol paediatric study until a juvenile rat toxicology study is complete and PK, safety and efficacy are evaluated in the adult population. An age-appropriate formulation will be developed. A waiver was granted for studies in children less than 6 months because of potential incomplete development of the BBB in this age group.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. 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.

- Tabular overview of clinical studies

Table 1 provides an overview of studies included in this application.

Table 1 Scope of clinical development program for naloxegol

Clinical Biopharmaceutic and Pharmacology studies	
Relative BA/BE, and food interaction	3 studies (08-PNL-04, D3820C00025* and D3820C00018)
Pharmacokinetic, proof of mechanism and initial tolerability	3 studies (05-IN-0X001**, 07-IN-NX-002 and D3820C00020)
ADME	1 study (D3820C00001)
Pharmacokinetic – intrinsic factors	2 studies (D3820C00009 and D3820C00010)
Pharmacokinetic – extrinsic factors (drug/drug interaction)	4 studies (D3820C00011***, D3820C00012, D3820C00015, and D3820C00032)
Pharmacodynamic (TQT)	1 study (D3820C00014)
Phase II study	
07-IN-NX003	
No. and type of randomized patients:	Of the 208 patients randomized, 194 completed the placebo run-in and entered the double-blind study period: naloxegol 5mg n=33, 25mg n=30, 50mg n=35 and placebo n=96. Efficacy data was derived for the modified ITT population, which consisted of 185 patients.
Doses and duration of treatment:	Naloxegol in aqueous solution 5, 25 or 50 mg once daily, 4 weeks
Condensed objective:	Efficacy and safety and tolerability to find an effective dose and PK of naloxegol in patients
Phase III studies	
D3820C0004	
No. and type of randomized patients:	652 patients were randomized with confirmed OIC and on stable opioid regimen, and received the following treatment: naloxegol 12.5 mg n=217, 25 mg n=218 and placebo n= 217.
Doses and duration of treatment:	Naloxegol tablet 12.5 mg or 25 mg once daily, 12 weeks
Primary objective:	Compare the efficacy of naloxegol 12.5 and 25 mg with placebo in the treatment of patients with OIC
D3820C0005	
No. and type of randomized patients:	700 patients were randomized with confirmed OIC and on stable opioid regimen, and received the following treatment: naloxegol 12.5 mg n=233, 25 mg n=234 and placebo n= 233
Doses and duration of treatment:	Naloxegol tablet 12.5 mg or 25 mg once daily, 12 weeks
Primary objective:	Compare the efficacy of naloxegol 12.5 and 25 mg with placebo in the treatment of patients with OIC
D3820C0007	
No and type of randomized patients:	302 patients rolled over from Study 04 and continued to receive the following treatments as originally assigned in Study 04: naloxegol 12.5 mg n=97, 25 mg n=99 and placebo n= 106
Doses and duration of treatment:	Naloxegol tablet 12.5 mg or 25 mg once daily, 12 weeks
Primary objective:	Compare naloxegol 12.5 and 25 mg with placebo regarding long-term (ie, additional 12 weeks) safety and tolerability in the treatment of opioid OIC using descriptive statistics

D3820C0008	
No and type of randomized patients:	844 randomized patients. 84 patients rolled over from Study 05 or Study 07, 760 newly randomized patients.
Doses and duration of treatment:	Randomly-assigned open-label naloxegol tablet 25 mg once daily or Usual Care treatment, 52 weeks
Primary objective:	Assess the long-term (ie, 52-week) safety and tolerability of naloxegol 25 mg.
D3820C0006	
No and type of randomized patients:	In Part A: 44 patients enrolled with cancer pain and reported OIC and 14 randomized and received once daily treatment: naloxegol 12.5 mg n=5, 25 mg n=5 and placebo n=4. In Part B: 9 Patients (7 in US and 2 in EU) continued in the active treatment extension: naloxegol 12.5 mg n=3, naloxegol 25 mg=6.
Doses and duration of treatment:	Part A: Naloxegol tablet 12.5 mg or 25 mg once daily, for 4 weeks Part B: additional 12 weeks naloxegol tablet 12.5 mg or 25 mg once daily, placebo patients from Part A were allocated to 25 mg naloxegol
Primary objective:	Compare the efficacy of naloxegol 12.5 and 25 mg with placebo in the treatment of cancer-pain patients with OIC
D3820C00028	A single visit, cross-sectional, qualitative interview study of 66 patients, to verify the appropriateness and relevance of stool symptom screener questions included in the Baseline Laxative Response Status Questionnaire (BLRSQ, used to define the patient's baseline laxative response status).

*Study 25 had intrinsic factor components (race and age),
** Study 05-IN-0X001 included PD components (morphine-induced miosis and oral cecal transit time [OCTT]),
*** Study 11 included a PD component (morphine-induced miosis)
ADME: Absorption, distribution, metabolism and excretion, BA: bioavailability, BE: bioequivalence.
For Tabulated listing of all clinical studies in the submission, see Module 5.2.

2.4.2. Pharmacokinetics

Absorption

Naloxegol undergoes rapid absorption with peak plasma concentrations attained less than 2 h after single doses of 5 to 1000 mg, and twice daily doses of 25 to 250 mg for up to 8 days. A secondary plasma concentration peak for all naloxegol formulations was observed in a number of volunteers approximately 0.4 to 3 h after the first peak, and was more prominent at lower doses (8 mg to 125 mg), which is likely due to enterohepatic recycling.

Naloxegol exposure is dose proportional at therapeutic doses. Following multiple dosing, steady state is achieved within 2 to 3 days, and minimal accumulation is observed with once daily dosing.

No absolute bioavailability data were provided. However, the results of the mass balance study indicate that the bioavailability might be 60%, provided that no degradation of the parent compound occurs in the faeces. However, metabolites M13, M10, M7 and M1 have been detected in plasma. M12 is formed by oxidation of M13 and M4 is formed by oxidation of M9, the product of demethylation of the PEG chain shown to be produced by CYP3A in vitro. In addition, the applicant further provided information that all identified metabolites are not formed by reductive processes, as such limiting the probability that these have been formed due to degradation of naloxegol in the faeces. Only for the remaining unidentified component (MX1) this is not clear; however, as this component represents only 2.2% of dose, it is considered unlikely that this would change the conclusions significantly.

Both naloxegol and naloxegol oxalate drug substance show high solubility in aqueous media from pH 1 to pH 7.5, thus ensuring good solubility of naloxegol in the stomach as well as in the small intestine. According to the Biopharmaceutical Classification System (BCS) Classification, based on the results of the pH solubility study, naloxegol and naloxegol oxalate are considered as highly soluble drug substances. Available permeability data suggest that naloxegol has a low permeability according to the BCS

Classification. Thus, naloxegol is classified as a BCS class III compound and for this type of drug substance, the drug absorption (permeability) is rate limiting and not the dissolution of the drug product.

Naloxegol exposure is significantly affected by co-administration with food: exposure increases by 42% to 55% and maximum plasma concentration increase by 30% to 47% when a 25 mg dose of naloxegol is administered after eating a meal, compared with fasting conditions. The magnitude of the increase for both AUC and Cmax appeared to be similar for all tablet formulations tested, for both the 12.5 mg and 25 mg tablet, and between Japanese and Western volunteers. This is described in an appropriate way in the SmPC since naloxegol should be administered in the morning, approximately 1 hour prior to eating, in clinical practice to achieve similar exposure as was observed in the Phase III program.

Distribution

After absorption, naloxegol plasma concentrations decline bi-exponentially: naloxegol is distributed into a central and a peripheral compartment, with typical values for apparent volume of 160 L and 266 L, respectively). The mean apparent volume of distribution during the terminal phase (Vz/F) ranged approximately from 968 L to 2140 L across dosing groups and studies. The volume of distribution suggests extra-vascular distribution. Results from a QWBA (Quantitative Whole Body Autoradiography) study in the rat and the lack of antagonism of CNS opiate effects in humans at naloxegol doses less than 250 mg, indicate minimal distribution of naloxegol into the CNS.

Plasma protein binding of naloxegol in humans is low and the fraction unbound ranged from 80% to 100%. No data were provided concerning the protein binding in renal/hepatic impaired patients nor in the target population. However, in view of the low degree of plasma protein binding, this is considered to be of no issue.

Elimination

The primary route of naloxegol elimination is via hepatic metabolism, with renal excretion playing a minimal role.

In vitro data indicate that naloxegol is a substrate for cytochrome P450 3A4 (CYP3A4) and that CYP3A is the major CYP enzyme responsible for the metabolism of naloxegol Naloxegol is also a substrate of the P-gp transporter, which likely plays a significant role in limiting CNS exposure to naloxegol and in its disposition.

In clinical studies, 6 metabolites were found in either feces, urine and plasma, none of which have been identified as unique or disproportionate human metabolites. The major plasma circulating species is naloxegol. None of the metabolites was present >10% of the plasma concentrations of parent or drug related material. These metabolites were formed via N-dealkylation (M1) and oxidation and partial loss of the PEG chain (M13, M7, M12, M10, and M4).

In the ADME study (Study D3820C00001), in which 27 mg of 14C-naloxegol was administered to healthy volunteers, most of the recovered radioactivity was found in feces, 67.7% of mean total recovery, with 16.0% of mean total recovery recovered in urine. This confirms that the primary elimination pathway is via fecal elimination. Parent naloxegol recovered in the feces accounted for only 16.2% of the dose (out of the total 67.7% recovered radioactivity in the feces). Parent naloxegol dose recovered in urine was only 5.90% of the dose. Mean cumulative recovery of radioactivity from urine and faeces (84.2%) was lower than expected. This is not in accordance with the recommendations of the Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev. 1), but the applicant discussed the lower radioactivity in the context of literature information showing lower recoveries for compounds predominantly excreted in the faeces.

The apparent divergence between studies, which could presume the presence of some metabolite(s) that represent a yet not identified important fraction of the radioactivity (ranging from 32% (at 0.5h) to 67% (at 6h)) has been adequately justified by the applicant. The metabolite profiling work used sample preparation and chromatographic separation followed by fraction collection and counting, which has lower sensitivity. A signal to noise cut-off (S/N>3) was applied, and then mass spectrometry (MS) detection was applied to the radiochemical peaks. Thus, at the dose used (27 mg) and with the amounts of radioactivity present in the plasma, not all the drug-related components may have been identified due to the sensitivity limits. This observation was confirmed by the results of study 07-IN-NX002 (250 mg dose group), during which a total of 17 metabolites have been identified (semi-quantitatively). It appears that the fraction of the radioactivity (ranging from 32% at 0.5h to 67% at 6h) is due to the presence of these metabolites. Most importantly, both studies show that there are no major circulating metabolites (<10% of drug-related material in plasma) and Study 07-IN-NX002 shows that there is no important difference at steady state. Therefore, the applicant's conclusion that no further characterisations are needed for the metabolites is endorsed.

At therapeutic doses, mean terminal elimination half-life values across the clinical pharmacology studies ranged from 6 to 11 h.

Dose proportionality and time dependencies

It appears that dose proportionality could be concluded for AUC and that Cmax tends to increases more than proportionally with increasing doses. However, by visual inspection of the graphs, positive deviation from proportionality is apparent only at doses of 250 mg and higher. Further analysis showed that as long as the dose ratio is less or equal to 2.29, dose proportionality is to be concluded. Therefore, dose proportionality can be concluded for both AUC0-∞ and Cmax in the dose range 12.5 mg – 50 mg.

Consistent with the terminal t1/2 values observed, steady state was reached after several days. The applicant concluded that no time-dependent changes have been observed for naloxegol. The apparent absence of steady state at day 8 in some of the subjects of Study 07-IN-NX002 is most probably due to interday variability. This was further confirmed by the comparison between the predicted and observed accumulation ratio at steady state which confirmed that naloxegol is not characterised by time-dependent PK.

Intra- and inter-individual variability

A moderate to high inter-individual variability (24.4-41.7%) and low intra-individual variability (ranging from 15.7% to 17.9%) have been noted for naloxegol.

Special populations

Patients versus volunteers

The findings in patients with OIC are consistent with those previously reported in healthy subjects. The justification provided by the applicant for the higher exposure as observed in the Phase III study (error and uncertainty in dosing and/or sampling times, different food consumption patterns, other underlying medical conditions in the Phase III patient populations, and/or other unknown factors) is acceptable as in the Phase IIb study no trend for higher exposure has been observed. Overall, naloxegol possesses predictable PK characteristics and does not require complex dosing regimens or dosing adjustments to achieve efficacy in patients with OIC.

Renal impairment

Renal clearance is a minor route of elimination for naloxegol, regardless of severity. However, pharmacokinetic characterization in patients with severe renal impairment should be considered even if the drug is eliminated mainly by metabolism.

A single-dose study (Study D3820C00009) to investigate renal impairment has been adequately performed and this single dose administration is sufficient since naloxegol exhibits linear and time-independent pharmacokinetics. We can observe that naloxegol exposure is higher in patients with renal impairment compared to patients with OIC with normal renal function. Renal impairment has a greater effect on the extent of exposure (AUC0-inf) compared to peak levels (Cmax) of naloxegol.

Overall, in severe renal impaired patients, AUC and Cmax of naloxegol increased by 117% and 84%, respectively, compared to patients with normal renal function. However, in 2 out of 8 patients (in both the moderate and severe renal impairment groups but not in the end stage renal failure group) up to 10-fold increases in the exposure of naloxegol were observed. As mentioned by the applicant, in these patients, renal impairment may adversely affect other clearance pathways (hepatic/gut drug metabolism, etc.) resulting in higher exposure. Therefore, the applicant agreed with a starting dose of 12.5 mg in patients with severe renal impairment (see section 4.2 of the SmPC). If side effects impacting tolerability occur, naloxegol should be discontinued. The dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient.

Exposure of naloxegol in end-stage renal disease (ESRD) patients on hemodialysis was similar to healthy volunteers with normal renal function.

Hepatic impairment

It is known that following oral administration naloxegol is extensively metabolized and is excreted primarily in the feces (~68% of the dose). Considering the important role of hepatic involvement in naloxegol elimination, decreased hepatic function was thought to potentially affect naloxegol exposure.

In this context, a single-dose study (study D3820C00010) to investigate hepatic impairment has been performed. A single dose administration is sufficient since naloxegol exhibit linear and time-independent pharmacokinetics. The effect of hepatic impairment on the pharmacokinetics of naloxegol was explored in subjects with mild (Childs-Pugh Class A) and moderate (Childs-Pugh Class B) impairment, compared to healthy matched volunteers following a 25 mg dose of naloxegol. In the study, Cmax values of naloxegol were similar (ratios of 0.95 and 1.00) and the AUC values were 0.83 in subjects with mild hepatic impairment and 0.82 in subjects with moderate hepatic impairment, when compared to volunteers with normal hepatic function. Less than 20% decrease in AUC and 10% decrease in Cmax were observed in patients with mild and moderate hepatic impairment (Child Pugh Class A and B). No dose adjustment is required for patients with mild to 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 nalogexol was not evaluated.

Gender

Gender was found to have no effect on AUC and Cmax and it was not identified as significant covariate. The SmPC mentions adequately that there is no gender effect on the pharmacokinetics of naloxegol.

Weight

Patients with high weight had somewhat increased naloxegol exposure but the difference in exposure is not considered as clinically meaningful. This is reflected correctly in section 5.2 of the SmPC with the

mention that naloxegol exposure was found to increase with increased weight but the effect on the pharmacokinetics of naloxegol is not clinically relevant.

Race

There is no clinically significant effect of race on the pharmacokinetic profile of naloxegol, although exposure was found lower in African-Americans/Blacks and, to a lesser extent, in Asians.

Elderly

Table presents the number of elderly patients that participated in the naloxegol clinical programme, in the age groups requested by the CHMP.

Table 2 Number of elderly patients involved across the clinical trial programme (Safety set)

eCTD Module	Age 65-74 number/ total number (all ages)	Age 75-84 number/ total number (all ages)	Age 85+ number/ total number (all ages)
Efficacy and Safety Studies[a]	207 / 2260	40 / 2260	0 / 2260
Human PK Studies[b]	13 / 457	5 / 457	0 / 457
Human PD Studies[c]	0 / 140	0 / 140	0 / 140
Biopharmaceutical Studies[d]	0 / 86	0 / 86	0 / 86

[a] Efficacy and safety studies include studies 04, 05, 06, 07, 08 and the Phase IIB study.
[b] Human PK studies include any Phase I study where naloxegol PK data was collected.
[c] Human PD studies include the TQT study (D3820C00014), the SAD study 05-IN-OX001 (orocecal transit time and pupillometry data) and the study D3820C00011 (pupillometry data), also including in the Human PK studies.
[d] Biopharmaceutical studies include studies 08-PNL-04, D3820C00025, D3820C00018 (also included in Human PK studies).
Note: Table includes unique patients included in the safety set, regardless of treatment group the patient is assigned.

A small effect of age on the pharmacokinetics of naloxegol (approximately 0.7% increase in AUC for every year increase in age) is observed and no dose adjustment is recommended for older people. Patients over 65 years of age have been represented in the phase III studies. Clinical studies of naloxegol did not include sufficient numbers of patients aged 75 years or over to determine whether they respond differently than younger patients, however, based on the mode of action of the active substance there are no theoretical reasons for any requirement for dose adjustments in this age group.

Children

No data in pediatric subjects is available.

Pharmacokinetic interaction studies

Four potential interactions with other drugs have been correctly studied by the applicant and the results of these investigations have been introduced into the SmPC.

In vitro data indicate that naloxegol is a substrate for cytochrome P450 3A4 (CYP3A4) and that CYP3A is the major CYP enzyme responsible for the metabolism of naloxegol. CYP450 enzymes are highly expressed in the intestinal epithelium and can be involved in pre-systemic drug metabolism along with first pass hepatic metabolism. Substances that inhibit or induce hepatic and gastrointestinal CYP3A4 can markedly affect plasma concentrations and bioavailability of CYP3A4 substrates and may result in significant drug interactions. Several in vivo drug interaction studies have been performed to investigate

the consequences of concomitant administrations of CYP3A4 inhibitors and inducers with naloxegol. Naloxegol is also a substrate of the P-gp transporter, which likely plays a significant role in limiting CNS exposure to naloxegol and in its disposition. Therefore, the impact of P-gp induction on naloxegol pharmacokinetics has also been explored.

The drug-drug interaction studies investigate the potential alterations of the disposition of naloxegol by drugs that interfere with CYP3A4 and P-gp as well as the potential interaction between naloxegol and morphine.

Ketoconazole – DDI study n° D3820C00012

The objective was to investigate the effect of ketoconazole on the bioavailability of naloxegol in healthy subjects. The study is an open-label, nonrandomized, fixed-sequence, 3-period, 3-treatment, single-dose, crossover study comparing the bioavailability of naloxegol when administered alone and in combination with ketoconazole.

A single dose of 25 mg naloxegol was administered on Day 1 (Treatment A) followed by a 2-day washout (Days 2 and 3). Once-daily doses of 400 mg ketoconazole were administered from Days 4 through Day 6 (Treatment B) and on Days 7 and 8 with coadministration of 25 mg naloxegol on Day 7 (Treatment C).

In the presence of ketoconazole, Geometric least-squares mean naloxegol AUC(0-t) was 13.00-fold (ratio, 90% CI: 13.00, 11.45 to 14.76) while Geometric least-squares mean naloxegol AUC(0-24) was 12.89-fold (ratio, 90% CI: 12.89, 11.42 to 14.56) that of naloxegol administered alone. For Cmax Geometric least-squares mean was 9.58-fold (ratio, 90% CI: 9.58, 8.10 to 11.33) that for naloxegol administered alone.

Co-administration of ketoconazole with naloxegol resulted in a high increase in the exposure of naloxegol. It can be clearly concluded that ketoconazole has an important impact on the PK parameters of naloxegol. Therefore, co-administration of naloxegol with ketoconazole, strong inhibitors of CYP3A4, is contraindicated. The SmPC adequately mentions that concomitant use of strong CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole) can significantly increase the exposure to naloxegol and is contraindicated.

Rifampin – DDI study n° D3820C00015

The objective was to investigate the effect of rifampin on the bioavailability of naloxegol in healthy subjects. The study is an open-label, nonrandomized, fixed-sequence, 3-period, 3-treatment, single-dose, crossover study comparing the bioavailability of naloxegol when administered alone and in combination with rifampin.

In Period 1, a single 25 mg dose of naloxegol (Treatment A) was administered orally on the morning of Day 1 followed by a 2-day washout (Days 2 and 3). In Period 2, once-daily doses of 600 mg rifampin (Treatment B) were administered from Days 4 through Day 12. In Period 3, a single dose of 25 mg naloxegol (Treatment C) was administered on the morning of Day 13.

Following once daily dosing of rifampin 600mg, naloxegol exposure is greatly decreased with AUC, Cmax and AUC(0-8) reduced by approximately 89% (ratio, 90% CI: 0.11, 0.095 to 0.12), approximately 76% (ratio, 90% CI: 0.24, 0.20 to 0.31) and approximately 87% (ratio, 90% CI: 0.13, 0.11 to 0.14) respectively.

Administration of rifampin significantly decreased exposure to naloxegol. The SmPC mentions that naloxegol is not recommended in patients who are taking strong CYP3A4 inducers (e.g. carbamazepine, rifampin, St. John's wort). Moreover, the SmPC specifies that concomitant use with P-gp inducers, which are also strong CYP3A4 inducers (e.g., carbamazepine, rifampin, St. John's wort) is not recommended.

Naloxegol is proved to be a substrate for CYP3A4 and also a substrate of the P-gp transporter. Rifampin, a potent CYP3A4 inducer and P-glycoprotein efflux inducer widely affects the PK of naloxegol. This is clearly mentioned in the SmPC that concomitant administration of naloxegol with strong inducers of CYP3A4 (and P-gp) is not recommended.

Diltiazem – DDI study n° D3820C00032

The objective was to investigate the effect of coadministration of diltiazem on the bioavailability of naloxegol in healthy subjects. The study is an open-label, nonrandomized, fixed-sequence, 3-period, 3-treatment, single-dose, crossover study comparing the bioavailability of naloxegol when administered alone and in combination with diltiazem.

In Period 1, a single 25-mg dose of naloxegol (Treatment A) was administered orally on the morning of Day 1 followed by a 2-day washout (Days 2 and 3). In Period 2, once-daily doses of 240-mg diltiazem extended release (XR) (Treatment B) were administered from Days 4 through Day 6. In Period 3, a single dose of 240-mg diltiazem XR plus a single dose of 25-mg naloxegol (Treatment C) was administered on the morning of Day 7 and a single dose of 240-mg diltiazem XR was administered on Day 8.

Co-administration of diltiazem with naloxegol resulted in 3.44-fold (ratio, 90% CI: 3.44, 3.19 to 3.72), 3.41-fold (ratio, 90% CI: 3,41, 3.16 to 3.68) and 2.86-fold (ratio, 90% CI: 2.86, 2.59 to 3.15) increase in naloxegol AUC(0-t), AUC(0-24) and Cmax, respectively.

Based on these results, a statistically significant effect of diltiazem on the pharmacokinetic of naloxegol can be concluded. The conclusions are that a dose-adjustment of naloxegol is recommended when co-administered with diltiazem and other moderate CYP3A4 inhibitors. This is described in an appropriate way in the SmPC which mentions that the starting dose for patients who are taking moderate CYP3A4 inhibitors (e.g. diltiazem, verapamil) is 12.5 mg once daily. The dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient.

Quinidine and morphine – DDI study n° D3820C00011

The objectives of the study n°D3820C00011 are to investigate the effects of quinidine (Part 1) and morphine (Part 2) on the bioavailability of naloxegol in healthy subjects. The study is a double-blind (with regard to quinidine administration), randomized, 2-part, 2-period, 2-treatment, single-dose, crossover study comparing the bioavailability of naloxegol when administered alone and in combination with quinidine and/or morphine.

In Part 1, Period 1 on Day 1, volunteers received a single oral dose of naloxegol 25 mg and quinidine placebo (Treatment A) or naloxegol 25 mg and quinidine 600 mg (Treatment B). Following a minimum 7-day washout period between dose administration, volunteers received the alternate treatment on Day 1 of Period 2.

Following a washout period of 7 days, a subset of volunteers returned to the clinic for Part 2. On Day 1 of Part 2, Period 3, volunteers received either Treatment C (a single oral dose of naloxegol 25 mg and quinidine placebo and i.v. administration of 5mg/70 kg morphine) or Treatment D (a single oral dose of naloxegol 25 mg and quinidine 600 mg and i.v. administration of 5mg/70 kg morphine). Following a minimum 7-day washout period between dose administration, volunteers received the alternate treatment on Day 1 of Period 4.

Co-administration of quinidine led to an increase in naloxegol AUC(0-t) by 1.41% (90% CI: 1.34 to 1.49), AUC(0-24) by 1.63% (90% CI: 1.48 to 1.80) and Cmax by 2.47% (90% CI: 2.19 to 2.78) compared with naloxegol alone.

The relative bioavailabilities of naloxegol after combined treatment with morphine compared with monotherapy were also estimated based on geometric mean ratios of AUC, AUC(0-24) and Cmax and their 90% confidence intervals (CIs). All 90% CIs were not entirely contained within the standard bioequivalence boundaries of 80.00 to 125.00 %.

Based on standard BE boundaries, co-administration of the P-gp inhibitor quinidine had clinically relevant effect on the PK of naloxegol. The SmPC specifies that P-gp inhibitors typically have concomitant effect on CYP3A4 that can be classified as weak (e.g. quinidine), moderate (e.g. diltiazem), or strong (e.g. ketocanozole). For all P-gp inhibitors (regardless of the degree of inhibition of P-gp), dosing recommendations should follow the concomitant CYP3A4 effect (e.g. dual strong CYP3A4/P-gp inhibitor follow strong CYP3A4 recommendation)

The 90% CIs of the geometric LS ratios of naloxegol Cmax (and not AUC) in the presence of morphine were slightly outside the standard bioequivalence range (0.78 – 1.19). However, the applicant states the geometric LS mean ratios of the naloxegol for Treatment C versus Treatment A showed that AUC, AUC(0-24) and Cmax in the presence of morphine were similar compared to naloxegol alone. Moreover, it should be noted that this was a post-hoc analysis, and the study was not powered to assess bioequivalence of the PK of naloxegol when co-administered with morphine.

In conclusion, the effect of potent inhibitor and inducer of CYP3A4 on the naloxegol pharmacokinetics is correctly investigated. The SmPC mentions correctly that concomitant administration of naloxegol with strong inhibitors of CYP3A4 (e.g. clarithromycin, ketoconazole) as well as with potent CYP3A4/P-gp inducers (e.g. carbamazepine, rifampin, St. John's wort) of CYP3A4 is contraindicated. The moderate CYP3A4 inhibitor used concomitantly with naloxegol (diltiazem) was adequately investigated. Increase in oral naloxegol exposure has been observed, leading to a dose-adjustment in the SmPC of naloxegol when co-administratered with moderate CYP3A4 inhibitors (e.g. diltiazem, verapamil). An additional in vivo drug interaction study with quinidine, a Pgp inhibitor and morphine was also carried out. As result dosing recommendations for naloxegol with all P-gp inhibitors have been mentioned in an appropriate way.

An adequate physiologically-based pharmacokinetics (PBPK) modelling was conducted to predict the effect of various inhibitors concomitantly administered in the phase III program. The PBPK model was constructed by integrating physiochemical properties, in-vitro metabolism data and in-vivo ketoconazole interaction information. The model was then applied and reasonably predicted other clinical DDI studies, ie, diltiazem and rifampin studies. The model has been then applied to moderate and weak CYP3A inhibitors which have been simulated for co-administration with naloxegol in phase 3 studies. The results obtained indicate that the AUC and Cmax ratios with strong, moderate and weak CYP3A/P-gp inhibitors and inducers were in agreement with the ratios observed in DDI studies of naloxegol.

As the dissolution and the solubility of naloxegol are pH independent, absorption of naloxegol is unlikely to be affected by drugs that increase gastric pH, eg, proton pump inhibitors (PPIs), H2-receptor antagonists, or antacids.

Concerning the potential interaction of naloxegol with oral contraceptives, the applicant has provided the results of the assessment based on in vitro inhibition and induction data to investigate the potential for these drug interactions. From the results of the assessment, naloxegol is considered unlikely to affect the efficacy of these medicinal products. Consequently, the applicant's position that no DDIs should be initiated for the hormonal contraceptive agents is endorsed.

2.4.3. Pharmacodynamics

Mechanism of action

Naloxegol functions as a peripherally-acting mu-opioid receptor antagonist in the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects on the central nervous system.

Naloxegol is a PEGylated derivative of the mu-opioid receptor antagonist naloxone. PEGylation reduces naloxegol's passive permeability and also renders the compound a substrate for the P-glycoprotein transporter. Due to poorer permeability and increased efflux of naloxegol across the blood-brain barrier, related to P-gp substrate properties, the CNS penetration of naloxegol is minimal.

In vitro studies demonstrate that naloxegol is a full neutral antagonist at the mu-opioid receptor. Naloxegol acts by binding to mu-opioid receptors in the GI tract targeting the underlying causes of OIC (i.e. reduced GI motility, hypertonicity and increased fluid absorption resulting from long-term opioid treatment).

Primary and Secondary pharmacology

Antagonism of morphine's peripheral and central nervous system effects

The capacity of naloxegol to antagonize the reduced gastrointestinal motility caused by morphine while not antagonizing of the effect of morphine on the central nervous system was investigated in Study 05-IN-OX001. Gastrointestinal motility was assessed by measuring orocecal transit time via the lactulose hydrogen breath test. Central nervous system effects were assessed by measuring antagonism of morphine-induced pupil constriction (ie, miosis).

Morphine was administered intravenously at a dose of 5 mg/70kg. Baseline orocecal transit times in healthy volunteers were established with the administration of lactulose with morphine placebo and naloxegol placebo. Volunteers then received lactulose with morphine and naloxegol and lactulose with morphine and placebo in a randomised crossover fashion, to determine the effect naloxegol on morphine-induced delay in orocecal transit time. In general, most subjects receiving intravenous morphine with placebo had at least a doubling in orocecal transit when compared to their baseline measurement. Large between subject variability was observed in orocecal transit times for morphine + placebo (21 to 290 minutes) as well as for morphine + naloxegol (20 to 245 minutes); thus, percent change in orocecal transit time was expressed relative to the subject's morphine + placebo value in an attempt to compensate for these between-subject differences. Median, minimum, and maximum percent changes in orocecal transit time when naloxegol was co-administered with morphine, compared to morphine alone, are presented in table 3.

Table 3 Percent change in orocecal transit times in subjects receiving naloxegol

		Percent reduction in orocecal transit time		
Naloxegol dose (mg)	N	Median	Minimum	Maximum
8	6	0	-12	23.1
16	4	0.4	-66.7	30.5
30	6	19.3	-60	44
60	5	13.4	-34.1	91.9
125	3	47.4	-24	60.8
250	4	23.9	14.4	60
500	5	26.4	-60	55
1000	5	29.2	17.3	69.2

Table 3 shows an increased percent reduction in the orocecal transit with increasing naloxegol dose with an apparent plateau at doses ≥125 mg.

Pupil diameter was also measured with a pupillometer under both morphine + naloxegol treatment and morphine + placebo treatment to determine the degree of antagonism of morphine-induced miosis by naloxegol. Individual cohorts received naloxegol doses of 8 mg, 15 mg, 30 mg, 60 mg, 125 mg, 250 mg, 500 mg, and 1000 mg.

Administration of morphine with placebo produced sustained miosis in the majority of subjects, as expected. Pupil diameter-time profiles after both the naloxegol and placebo treatments were essentially superimposable in all volunteers with the exception of 2 volunteers: 1 of 6 volunteers at the 250 mg dose level and 1 of 6 volunteers at the 1000 mg dose level, who had a possible attenuation of morphine-induced miosis after receiving morphine with naloxegol. Thus, naloxegol did not diminish morphine-induced miosis in a dose-dependent manner, and no diminution was observed at doses of 125 mg or lower.

Study D3820C00011 examined the effect of the co-administration of the P-gp inhibitor quinidine on the lack of antagonism of morphine-induced miosis exhibited by naloxegol. The peak miotic effect due to intravenous morphine administration was similar during both the naloxegol and the naloxegol + quinidine treatments, with peak decrease in pupil diameter of 1.09 mm in the absence of quinidine and 1.16 mm in the presence of quinidine.

Effect of naloxegol on QTc interval

There is no evidence that naloxegol prolongs the QT interval. In vitro, naloxegol was found to have no activity at the hERG-encoded potassium channel (IC50 >300 μM).

Results of a thorough QT study (D3820C00014) showed that single oral 25 mg and 150 mg doses of naloxegol did not prolong QTcF beyond 10 msec. The largest placebo-corrected mean change from baseline in QTcF occurred at 2 hours post-dose for the 25 mg dose and 1.5 hours dose for the 150 mg supra-therapeutic dose. The upper bounds of the 2-sided 90% CI were 2.9 msec for the 25 mg dose and 4.9 msec for the 150 mg dose, respectively. In addition, single 25 mg and 150 mg doses did not increase the incidence of QTcF intervals more than 450 msec and did not increase the QTcF interval more than 30 msec.

2.4.4. Discussion on clinical pharmacology

Naloxegol is PEG naloxol, also known as a PEGylated derivative of naloxone. It is a substrate of the P-glycoprotein (P-gp) transporter, which substantially limits its ability to cross the BBB. Naloxegol, by binding to μ-opioid receptors within the GI tract targets the underlying causes of OIC. With its antagonist effects essentially restricted to the opioid receptors located outside the CNS, naloxegol is expected to alleviate OIC without reducing the central analgesic effects of opioids.

The applicant has performed a comprehensive PK program, consisting of 14 Phase I studies. Naloxegol was administered to 398 healthy volunteers. In addition, 24 subjects with renal function impairment and 16 subjects with hepatic function impairment received naloxegol. Among the healthy volunteers, there were 40 Japanese volunteers that received naloxegol, including 6 elderly Japanese volunteers, in a study performed in Japan. Additional pharmacokinetic data is reported from 22 patients with opioid-induced constipation that receive naloxegol in a Phase IIb study.

Conventional studies with non-compartmental analysis as well as pop PK have been performed. The analytical methods are well validated and appear satisfactory in performance.

The bridging between the different formulations used during the development is done both by in vitro and in vivo comparative studies according to the document 'Questions & Answers: Positions on specific questions addressed to the pharmacokinetics working party' (EMA/618604/2008 Rev.8). Bioequivalence has been shown between the formulations used during phase I, II, III and the final marketing formulation.

2.4.5. Conclusions on clinical pharmacology

The Pharmacodynamic study data do not point to major safety concerns with regard to the use of naloxegol within the context of these studies. In a first study, it was demonstrated that PEG7-Naloxol antagonized morphine-induced delay in oral cecal transit time in a dose dependent manner. In addition, a second study could not detect reproducibly dose-dependent reversal of morphine-induced miosis symptoms. Statistically significant decreases in pupil diameter at 2 time points upon administration of naloxegol+quinidine compared to naloxegol only (with direction of change opposite to what was expected) were not considered to be clinically relevant. Assessment of QTcF versus RR intervals indicated that QTcF was adequately corrected for RR interval. No major safety issues were identified in the presented pharmacodynamics studies.

2.5. Clinical efficacy

Table 4 Clinical trial overview table

Study code and region	Study design	Treatment groups, planned duration and sample size	Gender M/F Median Age	Diagnosis inclusion criteria	Primary endpoint
07-IN-NX003 US, Germany, Romania, and Canada	A Phase IIb, randomised, doubleblind, placebo-controlled, multiple dose, dose escalation study	Once daily dosing of naloxegol 5 mg, 25 mg or 50 mg or placebo for 4 weeks. Naloxegol doses were evaluated in separate cohorts of patients; within each cohort patients were randomised to either placebo or naloxegol in 1:1 ratio. A total of 208 patients were randomised across the 3 cohorts, 207 of which received at least one dose of study drug in the placebo run-in period (71 patients in the 5 mg cohort [35 naloxegol and 36 placebo], 60 patients in the 25 mg cohort [31 naloxegol and 29 placebo] and 76 patients in the 50 mg cohort [37 naloxegol and 39 placebo]).	37.8% M 62.2% Median age 51y	*18 years of age or older, male or female. *Received a stable opioid regimen consisting of a total daily dose of 30 mg to 1000 mg of oral morphine, or equianalgesic amount(s) of 1 or more other opioid therapies , for a minimum of 2 weeks prior to screening for nonmalignant pain or cancer-related pain with no anticipated change in opioid dose requirement over the proposed study period as a result of disease progression. *Documented OIC with ≤ 5 SBMs confirmed over the 2-week OIC screening period (which corresponded with < 3 SBMs/week) with ≥ 1 self-reported symptom of hard/lumpy stools, straining, or sensation of incomplete evacuation/anorectal obstruction, as well as self-reported OIC (< 3 SBMs/week), and ≥ 1 associated symptom of hard/lumpy stools, straining, or sensation of incomplete evacuation/anorectal	The primary efficacy variable was the change from baseline in SBMs/week at Visit 6 (end of double-blind study treatment period Week 1) and defined as SBMs/week during the first week of double-blind study treatment period (between Visit 4 and Visit 6) minus baseline SBMs/week. Baseline was defined as the average SBMs/week during the 2-week OIC screening period. An SBM was defined as a BM without the use of laxatives in the previous 24 hours as recorded in the e-diary. Any BM occurring within 24 hours of laxative use was set to 0 in the calculation of number of SBMs and the day counted toward the total number of days in the study period. This was done because a laxative was considered a treatment failure (for that day) just as the lack of a SBM was.

				obstruction at the initial screening visit. *Willingness to stop all laxatives and other bowel regimens (see prohibited medications) throughout the 2-week OIC screening period and the 5-week treatment period, and to use only bisacodyl as rescue medication if a BM had not occurred within 72 hours of last recorded BM.	
D3820C00004 (Study 04) US, Germany, Slovakia, and Australia	A Phase III, randomised, doubleblind, placebo-controlled study	Once daily dosing of naloxegol 12.5 mg, 25 mg or placebo tablets for 12 weeks - 652 patients were randomised 1:1:1, of which 641 were in the ITT analysis set (placebo: 214, naloxegol 12.5 mg: 213, and naloxegol 25 mg: 214); 350 (54.6%) patients in the ITT analysis set were LIR.	38.7% M 61.3% F Median age 53y	(not limited to the criteria below) *Men and women who were between the ages of ≥18 and <85 years *Self-reported active symptoms of OIC at screening (<3 SBMs/week and experiencing ≥1 reported symptom of hard/lumpy stools, straining, or sensation of incomplete evacuation/anorectal obstruction in at least 25% of BMs over the previous 4 weeks) *Were receiving a stable maintenance opioid regimen consisting of a total daily dose of 30 mg to 1000 mg of oral morphine, or equianalgesic amount(s) of 1 or more other opioid therapies for a minimum of 4 weeks prior to screening for non-cancer-related pain with no anticipated change in opioid dose requirement over the proposed study period as a result of disease progression. *Willingness to stop all laxatives and	The primary efficacy variable is the response (responder/non-responder) to study drug during Weeks 1 to 12. A SBM was defined as a BM without the use of rescue laxatives (bisacodyl or enema) administered in the previous 24 hours. A responder to study drug during Weeks 1 to 12 was defined as a patient with at least 3 SBMs/week and at least a 1 SBM/week increase over baseline for at least 9 out of the 12 treatment weeks and 3 out of the last 4 treatment weeks during the double-blind treatment period demonstrated by the primary analysis in the ITT analysis set.

				other bowel regimens including prune juice and herbal products throughout the 2-week OIC confirmation period and the 12-week treatment period, and to use only bisacodyl as rescue medication if a BM had not occurred within at least 72 hours of the last recorded BM	
D3820C00005 (Study 05) US, Belgium, Croatia, Czech Republic, Hungary, Spain, Sweden, United Kingdom	A Phase III, randomised, doubleblind, placebo-controlled study	Once daily dosing of naloxegol 12.5 mg, 25 mg or placebo tablets for 12 weeks - 700 patients were randomised 1:1:1, of which 696 were in the ITT analysis set (placebo: 232, naloxegol 12.5 mg: 232, and naloxegol 25 mg: 232); 370 (53.2%) patients in the ITT analysis set were LIR.	36.6% M 63.4% F Median age 52.5y	(not limited to the criteria below) *Men and women who were between the ages of ≥18 and <85 years *Self-reported active symptoms of OIC at screening (<3 SBMs/week and experiencing ≥1 reported symptom of hard/lumpy stools, straining, or sensation of incomplete evacuation/anorectal obstruction in at least 25% of BMs over the previous 4 weeks) *Were receiving a stable maintenance opioid regimen consisting of a total daily dose of 30 mg to 1000 mg of oral morphine, or equianalgesic amount(s) of 1 or more other opioid therapies for a minimum of 4 weeks prior to screening for non-cancer-related pain with no anticipated change in opioid dose requirement over the proposed study period as a result of disease progression. *Willingness to stop all laxatives and other bowel regimens including prune juice and	The primary efficacy variable is the response (responder/non-responder) to study drug during Weeks 1 to 12. A SBM was defined as a BM without the use of rescue laxatives (bisacodyl or enema) administered in the previous 24 hours. A responder to study drug during Weeks 1 to 12 was defined as a patient with at least 3 SBMs/week and at least a 1 SBM/week increase over baseline for at least 9 out of the 12 treatment weeks and 3 out of the last 4 treatment weeks during the double-blind treatment period demonstrated by the primary analysis in the ITT analysis set.

				herbal products throughout the 2-week OIC confirmation period and the 12-week treatment period, and to use only bisacodyl as rescue medication if a BM had not occurred within at least 72 hours of the last recorded BM	
D3820C00007 (Study 07) US	Safety extension of Phase III doubleblind, randomised, placebocontrolled, parallel study (D3820C00004)	Once daily dosing of naloxegol 12.5 mg, 25 mg or placebo tablets for 12 weeks. Patients remained on the same randomised treatment/dose as in Study 04). Before study D3820C00007 was closed for enrolment, a total of 302 patients from the ITT set had continued to the double-blind extension from study D3820C00004. However, only 297 received study treatment in the extension study (placebo: 103, naloxegol 12.5 mg: 96, and naloxegol 25 mg: 98).	39.2% M 60.8% F Median age 53y	(not limited to the criteria below) *Must have completed the 12-week D3820C00004 study through Visit 8 *Provision of written informed consent prior to any study-specific procedures *Men and women who were to have been between the ages of ≥18 and <85 years at the time of the screening visit for Study D3820C00004 *Continued to receive a stable maintenance opioid regimen consisting of a total daily dose of 30 mg to 1000 mg of oral morphine, or equianalgesic amount(s) of 1 or more other opioid therapies *Willingness to continue abstinence from all laxatives and other bowel regimens including prune juice and herbal products throughout the additional 12-week treatment period, and to use only bisacodyl as rescue medication if a bowel movement (BM) had not occurred within at least 72 hours of the last recorded BM	The current study was primarily a safety study. Descriptive statistics by treatment group for the secondary efficacy variables were summarized at baseline (in Study D3820C00004), Weeks 12, 16, 24, and 26, as well as the change from baseline to each post-dose time point for the efficacy parameters (PAC-SYM and PAC-QOL).

2.5.1. Dose response study

Study 07-IN-NX003

This was a multicenter, international, randomized, double-blind, placebo-controlled, multiple-dose, dose escalation study of the efficacy, safety, and tolerability of NKTR-118 in patients with documented OIC. The diagnosis of OIC was confirmed during a 2-week screening period.

Methods

- Study participants

Patients needed to meet all of the following criteria for inclusion in the study:

  - Adult patients who received a stable opioid regimen (a total daily dose 30 – 1000 MEU), for minimum of 2 weeks prior to screening for non-malignant pain or cancer-related pain
  - Documented OIC with <5 SBMs confirmed over the 2-week OIC screening period with >1 self-reported symptom of OIC (hard/lumpy stools, straining, or sensation of incomplete evacuation/anorectal obstruction), as well as self-reported OIC (< 3 SBMs/week),

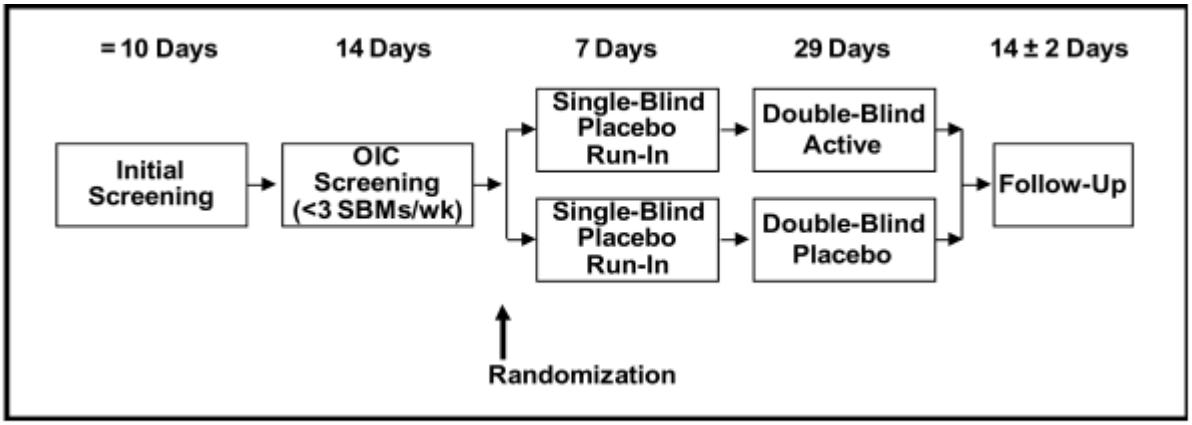
Patients presenting any of the following conditions were not included in the trial:

  - Fecal incontinence, irritable bowel syndrome, inflammatory bowel disease, intestinal obstruction, or other active medical disorders associated with diarrhea or intermittent loose stools or constipation;
  - Brain metastases, epidural metastases, malignant tumor of the brain, multiple sclerosis, or any other condition that may have affected the permeability of the blood-brain barrier.
  - History of ischemic heart disease or a screening ECG compatible with ischemic heart disease, or any other medical condition that may have unduly increased risk to the patient or may have affected the interpretation of study data (eg, inadequately controlled clinical depression, ventricular arrhythmias, poorly controlled seizure disorder).
  - Severe background pain (eg, typical average daily pain intensity rating of 7 to 10 on an 11-point NRS refractory to opioid therapy).

Treatments

All patients randomized following successful completion of the 2-week OIC screening period entered the 1-week placebo run-in period, during which they received a single morning dose of placebo. After the placebo run-in period, patients were received single daily oral doses of either placebo or NKTR-118, according to their randomization assignment, for 4 weeks. Patients randomized to active treatment were provided NKTR-118 as oral solution at a dose of 5 mg (Cohort 1), 25 mg (Cohort 2), or 50 mg (Cohort 3). A dose of 38 mg was planned for inclusion in Cohort 4; however, enrollment in this cohort was never initiated. The doses of NKTR-118 were originally scheduled to be 5 mg, 25 mg, 50 mg, and 100 mg QD. Upon review of safety and tolerability data from the 50 mg dose cohort, it was decided to complete enrolment and study participation for this dose cohort. It was suggested to take into consideration an intermediary dose of NKTR-118, such as 37.5 mg. After a preliminary analysis was performed on the first 3 groups (5, 25 and 50 mg), the Sponsor decided to end the study after completion of the third cohort.

Study 07-IN-NX003 Flow Chart



Objectives

Primary Objective

- Primary objective was to evaluate the efficacy of NKTR-118 at various dose levels, with efficacy defined as the change from baseline in the number of spontaneous bowel movements (SBMs) per week.

Secondary Objectives

- The main secondary objective was to evaluate the safety and tolerability of NKTR-118, thereby enabling identification of an effective dose that preserves opioid-conferred analgesia
- Delineate dose-response for NKTR-118 across a range of underlying opioid doses, with response defined as the change from baseline in SBMs/week
- Characterize the PK of NKTR-118 in patients

Outcomes/endpoints

Efficacy

Primary Efficacy Endpoint:

- The primary efficacy variable was the change from baseline in SBMs/week at Visit 6 (end of double-blind study treatment period Week 1) and defined as SBMs/week during the first week of double-blind study treatment period (between Visit 4 and Visit 6) minus baseline SBMs/week. Baseline was defined as the average SBMs/week during the 2-week OIC screening period.

Secondary Efficacy Endpoints:

- Change from baseline in SBMs/week during double-blind study treatment period Weeks 2, 3, and 4.
- Change from baseline in SBMs/week across the 28-day double-blind period.
- Time from first dose of the study treatment in the double-blind period to first laxation.
- Dose-response relationship with response defined as change from baseline in the number of SBMs/week.
- Clinical laboratory evaluation of FSH, LH, testosterone, prolactin, and estradiol.

- PAC-SYM, PAC-QOL, and SF-36 at Visit 4 (Day 1 of double blind treatment period prior to first dose of the study treatment), Visit 7 (Day 1 of Week 4 of double blind study treatment period), Visit 9 (end of double-blind study treatment period).

Secondary safety endpoints included the following:

- Opioid withdrawal symptoms as measured by the COWS scheduled 3 times during the trial (at the beginning of the placebo run-in period; two hours after the initial dose; three days after the initial dose
- Daily opioid requirement and mean and maximal daily NRS score
- Daily bisacodyl rescue medication
- Adverse events: TEAEs, SAEs, study discontinuation due to AEs, adverse events of special interest
- Clinical laboratory evaluation:

Pharmacokinetics:

The endpoints for the PK analyses included standard non-compartmental PK parameters derived from plasma concentration data.

Sample size

This study planned to enrol up to 4 sequential dose cohorts comprising approximately 240 patients. A common SD of 3.5 SBMs/week was selected based on published data from similar studies. It was assumed that the number of SBMs per week would increase more prominently among patients on NKTR-118 compared with patients receiving placebo with a mean difference of ≥2.5 SBMs/week. A sample size of 27 patients in each treatment group in the first 3 cohorts (5 mg, 25 mg, and 50 mg) had 80% power to detect a difference in means of 2.5 SBMs between NKTR-118 and placebo assuming a common SD of 3.5 SBMs with a 0.10 2-sided significance level using a Mann-Whitney test.

Randomisation

Each screened patient was assigned a unique patient number. Patients were randomized, received a unique randomization number, and entered the placebo run-in period followed by the 4-week randomized treatment period. Randomization was stratified by total daily opioid dose at screening in MEU (low, 30 to 100 MEU; high, > 100 to 1000 MEU).

Following database lock, it was identified that MEU conversion for baseline opioid use for stratification was not performed consistently by the study sites for some patients. Therefore, MEU conversion for baseline opioid use was recalculated.

Blinding (masking)

A computer-generated randomization scheme was stratified by baseline opioid use (low/high). Study medication (NKTR-118 and placebo) bottles, bottle cartons, and syringe cartons were prepared for dosing and labelled at least the following information: the protocol number, blinded name/code of the drug, the route of administration, the patient number, patient initials, date of dispensing, lot number, expiry date, and any required cautionary statements.

Syringes were labelled with the protocol number, blinded name/code of the drug, patient number, date of dispensing, and expiry date.

The site pharmacist and/or the designated staff who diluted study medication were the only people at the site handling the study medication bottles including: receipt at the site, weekly study medication dilution and preparation of the patient syringes, and drug bottle/kit accountability.

An unblinded site monitor monitored drug accountability and returned the drug accountability form, along with the used and unused bottles of study medication, to the study medication distributor where a second reconciliation was conducted and documented.

Study coordinators and blinded site monitors only reported on accountability of the patient oral syringes. Study coordinators and blinded monitors may have opened the syringe cartons, performed a count of returned oral syringes, and checked to see if plungers had been depressed (indicating dispensing of study medication by patient).

Statistical methods

Analysis of the primary endpoint was conducted based on the modified intent-to-treat (MITT) population. The primary endpoint was summarized by cohort and treatment group.

The Wilcoxon rank sum test was used to compare the treatment groups (NKTR-118 vs. placebo) within each cohort. The Wilcoxon signed rank test was used for the within group comparisons.

An exact Wilcoxon rank sum test was performed as a supplementary analysis for the primary endpoint to confirm that the normal approximation provides results sufficiently close to those of the exact test to give confidence in using the normal approximation for the Wilcoxon rank sum tests of all secondary endpoints.

The reported P values for Wilcoxon rank sum test and exact Wilcoxon rank sum test were sufficiently close throughout the efficacy endpoints analyses. Therefore the P values based on Wilcoxon rank sum test were reported in this clinical study report. Consistent with the protocol, an exact stratified Wilcoxon rank sum test (with a stratification factor of baseline opioid dose) was performed as a supplementary analysis for the primary endpoint.

Results

- **Participant flow and Numbers analyzed**

Patient disposition: all randomized patients							
N (%)	5 mg QD		25 mg QD		50 mg QD		Total N=208
	Placebo N=36	NKTR-118 N=36	Placebo N=29	NKTR-118 N=31	Placebo N=39	NKTR-118 N=37	
mITT	31 (86.1)	31 (86.1)	27 (93.1)	29 (93.5)	37 (94.9)	30 (81.1)	185 (88.9)
Safety	36 (100)	35 (97.2)	29 (100)	31 (100)	39 (100)	37 (100)	207 (99.5)
PK	10 (27.8)	5 (13.9)	8 (27.6)	12 (38.7)	9 (23.1)	6 (16.2)	50 (24.0)
Received at least 1 dose placebo run-in medication							
Completed Placebo Run-in	32 (88.9)	33 (91.7)	27 (93.1)	30 (96.8)	37 (94.9)	35 (94.6)	194 (93.3)
Withdrew from Placebo Run-in	4 (11.1)	2 (5.6)	2 (6.9)	1 (3.2)	2 (5.1)	2 (5.4)	13 (6.3)
Primary reason for withdrawal							
Withdrew Consent	2 (50.0)	1 (50.0)	0	0	0	0	3 (23.1)
AE	0	0	0	1 (100)	0	1 (50.0)	2 (15.4)
Lost to Follow-up	1 (25.0)	0	0	0	0	0	1 (7 .7)
Sponsor Decision	0	0	1 (50.0)	0	1 (50.0)	0	2 (15.4)
Inclusion/Exclusion Criteria Not Met	0	1 (50.0)	1 (50.0)	0	0	0	2 (15.4)
Other	1 (25.0)	0	0	0	1 (50.0)	1 (50.0)	3 (23.1)
Received ≥1 Dose Double-Blind Medication							
Completed double-blind	27 (75.0)	28 (77.8)	27 (93.1)	28 (90.3)	31 (79.5)	21 (56.8)	162

							(77.9)
Withdrew from double-blind	5 (13.9)	5 (13.9)	0	2 (6.5)	6 (15.4)	14 (37.8)	32 (15.4)
Primary Reason for Withdrawal							
Withdrew Consent	2 (40.0)	0	0	1 (50.0)	0	3 (21.4)	6 (18.8)
AE	1 (20.0)	1 (20.0)	0	1 (50.0)	2 (33.3)	10 (71.4)	15 (46.9)
Lost to Follow-up	0	1 (20.0)	0	0	0	0	1 (3 .1)
Investigator Decision	2 (40.0)	0	0	0	0	0	2 (6 .3)
Sponsor Decision	0	1 (20.0)	0	0	1 (16.7)	0	2 (6.3)
MSOW	0	1 (20.0)	0	0	0	0	1 (3.1)
Inclusion/Exclusion Criteria Not Met	0	1 (20.0)	0	0	1 (16.7)	0	2 (6.3)
Other	0	0	0	0	2 (33.3)	1 (7.1)	3 (9.4)
Entered Follow-up Period							
Completed Follow-up	26 (72.2)	28 (77.8)	27 (93.1)	28 (90.3)	31 (79.5)	20 (54.1)	160 (76.9)
Withdrew from Follow-up	1 (2.8)	0	0	0	0	1 (2.7)	2 (1.0)
Primary Reason for Withdrawal							
AE	0	0	0	0	0	1 (100)	1(50.0)
Other	1(100)	0	0	0	0	0	1 (50.0)

More patients were enrolled in the high-baseline opioid stratum (n = 116) compared with the low-baseline opioid stratum (n = 91). A slightly higher proportion of patients in the high-baseline opioid stratum completed the placebo run-in (97.4% vs. 88.0%).

The majority of patients (160 [76.9%]) completed the study, including the follow-up period. A similar number of patients in the low- and high-baseline opioid stratums (71 [77.2%] and 91 [78.4%], respectively) completed the double-blind study period.

Thirty-two (15.4%) patients withdrew during the double-blind period. The most frequent reason for discontinuation was AEs (15 patients [46.9%]); the majority of these patients (10 [71.4%]) were in the NKTR-118 treatment arm of Cohort 3 (50 mg) and in the high-baseline opioid stratum (8 patients [72.7%]).

Recruitment

The study was initiated 04 January 2008 (First patient enrolled) and finished at 23 March 2009 (Last patient completed).

Conduct of the study

The original protocol was issued on 20 Sep 2007 and was amended 6 times.

The finalized SAP indicated that the MITT is the primary analysis population. The SAP indicated that analysis of the efficacy endpoints will be also conducted on per-protocol population as a secondary analysis. The finalized SAP indicated that the secondary endpoint of time to first laxation will be calculated in days. After finalization of the SAP, it was decided that this endpoint will be calculated in hours in order to be consistent with published literature.

According to the SAP, no statistical testing of time to first SBM was planned. However, post-hoc inferential comparison of NKTR-118 and placebo within each cohort was conducted using log-rank test and corresponding P values were presented.

A Kaplan-Meier summary of time to withdrawal due to bisacodyl rescue failure which was planned in the final SAP was not produced. There was no subject who withdrew due to bisacodyl rescue failure. For the COWS scores categorical analysis, the SAP specified that Cochran-Mantel test will be used. However, after finalization of the SAP and during programming of the analysis it became use Fisher's exact test instead.

According to the protocol, all statistical testing will be conducted at the 0.10 two-sided significance level. During development of the SAP and prior to unblinding of the data, it was decided to conduct statistical tests at the 0.05 two-sided significance level.

Major Protocol Violations Identified at Study Conclusion, was not produced because after reviewing all protocol deviations, all violations were considered equally important and it was decided not to differentiate between major and minor protocol deviations.

Following database lock, it was identified that MEU conversion for baseline opioid use for stratification was not performed consistently by the study sites for some patients. Therefore, MEU conversion for baseline opioid use was recalculated and corrected tables and figures were generated.

For the AE, the SAP specified using entire safety population. Only those patients were included who entered the double-blind period since these were more relevant to double-blind study treatment.

The SAP specified NRS scores to be analyzed in the OIC screening, placebo run-in, and double blind periods. NRS scores were not collected during OIC screening, hence placebo run-in was treated as baseline in the analysis.

Baseline data

The majority of patients in the MITT population were female (62.2%) and Caucasian (86.5%). The mean patient age was 49.7 years, with a range of 21 to 80 years. Baseline mean PT and PTT were similar across all cohorts and active and placebo patients. A total of 194 patients received at least 1 dose of double-blind study medication.

No patients tested positive for urinary cocaine at baseline and 1 (0.5%) placebo patient in Cohort 3 (50 mg) tested positive for urinary cannabinoids at baseline; however, 7 patients (3.8%) tested positive for urinary amphetamines. Distribution of positive patients was across all treatment groups except the NKTR-118 arm of Cohort 1 (5 mg).

Baseline Opioid Stratum: mITT Population							
	5 mg QD		25 mg QD		50 mg QD		Total
	Placebo	NKTR-118	Placebo	NKTR-118	Placebo	NKTR-118	
Baseline Opioid Stratum	N=31	N=31	N=27	N=29	N=37	N=30	N=185
Low n (%)	10 (32.3)	12 (38.7)	13 (48.1)	12 (41.4)	18 (48.6)	13 (43.3)	78 (42.2)
High n (%)	21 (67.7)	19 (61.3)	14 (51.9)	17 (58.6)	19 (51.4)	17 (56.7)	107 (57.8)
Mean height (cm)	167.4	169.9	169.3	172.0	170.4	166.5	169.3
Mean weight (kg)	89.1	87.9	84.9	91.6	87.0	93.5	89.0

Outcomes and estimation

Primary endpoint

The primary endpoint for this study was change from baseline in SBMs/week to the end of the first week of double-blind study drug administration.

For Cohort 1 (5 mg), the mean change in SBMs/week from baseline to the end of Week 1 was 2.6 for NKTR-118 patients and 1.8 for placebo patients. The primary endpoint for the 5 mg group was not statistically significant.

For Cohort 2 (25 mg), the mean change in SBMs/week from baseline to the end of Week 1 was 3.6 for NKTR-118 patients and 1.9 for placebo patients. The primary endpoint for the 25 mg group was statistically significant (P = 0.0020).

For Cohort 3 (50 mg), the mean change in SBMs/week from baseline to the end of Week 1 was 4.4 for NKTR-118 patients and 1.9 for placebo patients. The primary endpoint for the 50 mg group was statistically significant (P = 0.0001). It is important to note that for all the analyzed cohorts (Cohort 1, 2, and 3), statistically significant effects were observed (p<0.0001; p<0.0001; and 0.0011) in the placebo subgroups.

In addition to the primary efficacy analysis, the change in weekly SBM frequency was also studied. The mean number of SBMs/week across the 28-day double-blind period increased with each successive dosing cohort, from 4.2 SBMs/week for 5 mg patients to 4.6 SBMs/week for 25 mg patients to 6.2 SBMs/week for 50 mg patients. However the formal statistical analysis was not performed.

Secondary Endpoints

- Change from Baseline in SBMs/Week during Weeks 2, 3, and 4

For Cohort 1 (5 mg), the mean change in SBMs/week from baseline during Weeks 2, 3, and 4 were not statistically significant for NKTR-118 patients compared to placebo patients (p= 0.8793, p=0.3529, p= 0.7618, respectively). For Cohorts 2 (25 mg) and 3 (50 mg), the mean change in SBMs/week from baseline during Weeks 2, 3, and 4 (except week 2, for Cohort 2, p=0.0961) were statistically significant.

For Cohort 2 (25 mg), the mean change in SBMs/week from baseline during Weeks 3 and 4 were significant (P =0.0092 and P = 0.0002, respectively). For Cohort 3 (50 mg), the mean change in SBMs/week from baseline during Weeks 2, 3, and 4 were statistically significant (P = <0.0001, P = <0.0001, and P = 0.0002, respectively).

- Change from Baseline in SBMs/Week Across the 28-day Double-Blind Period

For Cohort 1 (5 mg), the mean change in SBMs/week from baseline across the 28-day double blind period was not statistically significant. For Cohort 2 (25 mg), the mean change was 3.2 for NKTR-118 patients and 1.7 for placebo patients. This secondary endpoint for the 25 mg group was statistically significant (P = 0.0022). For Cohort 3 (50 mg), the mean change was 4.6 for NKTR-118 patients and 1.2 for placebo patients. This secondary endpoint for the 50 mg group was statistically significant (P = <0.0001).

- Time to First Laxation

The time to first laxation was not statistically significantly different between NKTR-118 (5 mg) and placebo groups, with respective median time to first laxation of 6.2 vs 28.2 hours. The time to first laxation was statistically significantly shorter in the NKTR-118 (25 mg) and (50 mg) cohorts compared to placebo with respective P = 0.0012 and P = 0.0016. The median time to first laxation for NKTR-118 (25 mg) vs placebo was 6.6 vs 48.6 hours and was 2.9 vs 44.9 hours for NKTR-118 (50 mg) vs placebo.

Laboratory Evaluation of FSH, LH, Testosterone, Prolactin, and Estradiol

There were no meaningful changes in the levels of the hormones evaluated in this study.

- Health Outcomes Assessments: PAC-SYM, PAC-QOL, and SF-36

The majority of mean PAC-SYM scores at all post dose time points for abdominal symptoms, rectal symptoms, stool symptoms, and the total mean scores were <2 at most double-blind time points, indicating mild gastrointestinal (GI) symptoms for placebo and NKTR-118 patients. The group receiving NKTR-118 5 mg did not differ from the placebo group at any of the time points (double blind week 2 and 4) for any of PAC-SYM scale scores. The group receiving NKTR-118 25 mg exhibited significant statistical differences in terms of: Rectal symptoms (p=0.0496), Stool symptoms (p=0.0100) and Total score (p=0.0163) at Visit 7 (double blind week 2); as well as in terms of Stool symptoms (p=0.0335) at Visit 9 (double blind week 4). Except for Rectal symptoms at Visit 9 (double blind week 4) (p=0.0116), the

administration of NKTR-118 50 mg did not bring about significant changes in comparison to placebo as measured by the PAC-SYM scale. NKTR-118 patients in 2 cohorts (except 5 mg cohort) reported statistically significant greater satisfaction compared with placebo patients as measured by the PAC-QOL. At the same time, in the other subscales of PAC-QOL (Physical Discomfort, Worries/Concerns, Psychosocial Discomfort) no significant differences were observed in comparison to placebo for all analyzed doses of NKTR-118, except for Physical Discomfort in the NKTR-118 25 mg group at Visit 7 (double blind week 2). NKTR-118 25 mg patients experienced statistically significant SF-36 scale scores that were higher than placebo for physical functioning at Visit 7 (DB Week 2), mental health at Visit 7 (DB Week 2) and Visit 9 (DB Week 4), and social functioning at Visit 9 (DB Week 4). At any other post-dose time points there were no statistically significant differences between NKTR-118 and placebo groups.

Post hoc analysis showed that the proportion of responders (i.e., patients who showed an increase of ≥ 2 SBMs/week from baseline) across the 28-day double-blind period was significantly higher in the NKTR-118 group vs. placebo group in both the 25 mg (75% vs. 26%) and 50 mg cohorts (92% vs. 29%; P = 0.0003 and P = 0.0001, respectively). However, the difference between the NKTR-118 and placebo groups in the 5 mg cohort was not statistically significant.

Pharmacokinetics results

NKTR-118 was rapidly absorbed independent of dose and duration of dosing. Systemic exposure to NKTR-118 was dose proportional, and the elimination rate was independent of dose. Pharmacokinetic steady-state was achieved rapidly with no appreciable accumulation occurring after QD dosing. There were no differences in PK characteristics between males and females.

Glucuronidation of NKTR-118 is a minor metabolic pathway. No metabolite exceeded 10% in abundance relative to parent NKTR-118 in plasma or urine and no metabolite accumulated after 28 days of dosing. Further, no indication of induction or inhibition of any metabolic pathway was observed during the 28-day dosing period. The observed lack of accumulation after QD dosing is consistent with the trend in pre-dose concentration values, dose proportional PK, and apparent terminal elimination half life (t½) values typically less than the dosing interval observed in this study. The following table shows the mean NKTR-118 PK parameters in the evaluable PK population All of these findings are consistent with those previously reported following administration of NKTR-118 in healthy subjects. Overall, NKTR-118 possesses predictable PK characteristics and does not require complex dosing regimens or dosing adjustments to achieve efficacy in patients with OIC.

Mean (CV%) NKTR-118 PK Parameters: Evaluable PK Population

Day	Dose(mg)	N	Tmax(hr)	Cmax (ng/mL)	AUC(0-24) (hr*ng/mL)	T1/2(hr)
1	5	5	1.7 (84.7)	9.1 (52.2)	34.01 (48.8)	NC
	25	12	1.5 (61.1)	70.6 (42.3)	327.7 (47.7)	NC
	50	5	1.5 (91.3)	123.7 (36.3)	426.8 (22.1)	NC
28	5	4	1.5 (81.7)	8.0 (49.2)	39.0 (23.1)	17.4 (8.3)
	25	9	1.4 (43.9)	81.1 (45.7)	334.8 (51.4)	14.1 (4.9)
	50	4	1.6 (101.7)	100.0 (41.9)	403.6 (36.7)	20.3 (10.3)

N: number of patients with evaluable PK data. CV%: Coefficient of variation, expressed as percent of mean value. NC: not calculated for Day 1.

Summary of main efficacy results

This study demonstrated that NKTR-118 can effectively reverse OIC, without compromising analgesia or inducing withdrawal symptoms, in patients who received a stable opioid regimen across a wide range of opioid doses (30 mg to 1000 mg daily of oral morphine, or equianalgesic amounts).

When PK and efficacy data were compared, an exposure response relationship between the primary efficacy endpoint and NKTR-118 systemic exposure was identified. An increase of approximately 4 SBMs/week from baseline that was sustained throughout the study was associated with the 2 higher doses of NKTR-118 (25 mg and 50 mg).

During double-blind treatment, NKTR-118 patients had more SBMs than placebo patients at all post dose time points. The mean number of SBMs/week increased with each NKTR-118 dose, from 4.2 SBMs/week (5 mg) to 4.6 SBMs/week (25 mg) to 6.2 SBMs/week (50 mg). NKTR-118 in Cohort 1 (5 mg) was not more effective than placebo in increasing SBMs among low-baseline opioid stratum patients; however, NKTR-118 was more effective than placebo in increasing SBMs among the high-baseline opioid stratum patients. NKTR-118 patients in Cohort 2 (25 mg) and Cohort 3 (50 mg) had more SBMs/week compared with placebo patients in both the low and high-baseline opioid strata.

2.5.2. Main studies

Study 04 (Study Code D3820C00004)

This was a Phase III, multi-centre, double-blind, randomized, placebo-controlled, parallel group study of 2 doses of NKTR-118 (25 mg and 12.5 mg) and placebo in patients with non-cancer-related pain and Opioid-Induced Constipation (OIC), conducted in Australia, Germany, Slovakia, and the US. The study duration was up to 18 weeks, consisting of an initial screening period lasting up to 2 weeks, a 2-week OIC confirmation period, during which the diagnosis of OIC and stability of the opioid regimen were confirmed, a 12-week treatment period, and a follow-up visit 2 weeks after the last dose of study drug.

Methods

Study Participants

The naloxegol phase III program targeted recruitment of a patient population that is representative of the intended OIC population.

Main inclusion criteria

The study enrolled adult patients:

- whose OIC diagnosis had been confirmed prospectively with a 2 week daily diary;
- who were receiving a stable maintenance opioid regimen for non-cancer-related pain;
- and who reported a history of <3 SBMs/week and at least 1 OIC-associated symptom at screening and confirmed diagnosis of OIC.

Main exclusion criteria

Patients presenting any of the following conditions were not included in the trial:

- patients with pre-existing constipation for reasons other than opioid treatment, or patients who had diarrhea;
- patients with potentially weakened integrity of the GI wall, due to risk for bowel perforation;
- patients who required concomitant prohibited medication (ie, strong inhibitors of CYP3A4 or p-GP, opioid antagonists and mixed agonists/antagonists, and laxatives);
- patients with potential for blood-brain barrier disruptions (eg, active multiple sclerosis, advanced Alzheimer's disease, uncontrolled epilepsy);

- patients with cancer pain;
- and patients with recent history of myocardial infarction (MI), symptomatic congestive heart failure, or any other overt CV disease.

Target subject population and sample size

Adult patients who were receiving a stable maintenance opioid regimen (total daily dose of 30 to 1000 mg of oral morphine, or equianalgesic amount[s] of 1 or more other opioid therapies for a minimum of 4 weeks) for non-cancer-related pain and who reported a history of <3 spontaneous bowel movements (SBMs)/week and at least 1 OIC associated symptom at screening and had a confirmed diagnosis of OIC were eligible to be randomized.

Confirmed OIC was defined as: documented <3 SBMs/week on average over the 2-week OIC confirmation period. Patients with uneven distribution of SBMs across the 2-week OIC confirmation period (0 SBMs in 1 week with ≥4 SBMs in the other week) were to be excluded. In addition to the SBM frequency criterion, patients must have reported ≥1 of the following symptoms in at least 25% of the bowel movements (BMs) recorded in the electronic diary during the OIC confirmation period: Bristol Stool Scale stool type 1 or 2; moderate, severe, or very severe straining; incomplete BM. Patients who had 0 BMs over the 2-week OIC confirmation period were not randomized.

In addition, a minimum of 50% of patients were to meet the following criteria for being laxative inadequate responders (LIR): Patient must have been taking 1 laxative class for a minimum of 4 days out of the 14 days prior to the screening visit and report moderate, severe, or very severe symptoms in at least 1 of the 4 stool symptom domains to qualify for assessment of LIR.

To provide an adequate power to detect a treatment difference in the LIR subgroup (assuming LIR is 50% of the total study population), it was recommended that 210 patients per group (total 630 patients for 3 treatment groups) be randomized to the study.

Treatments

NKTR-118 12.5 or 25 mg tablets, or matching placebo, were administered once daily. The duration of treatment was 12 weeks

Objectives

Primary objectives

The primary objective of this study was to compare the efficacy of naloxegol 12.5 mg and 25 mg with placebo in the treatment of patients who have OIC.

Secondary objectives

The secondary objectives were to compare naloxegol 12.5 mg and 25 mg with placebo on the daily signs and symptoms associated with OIC (straining, sensation of incomplete evacuation, and stool consistency), symptoms of constipation, and quality of life.

Safety objective

The safety objectives were to assess the safety and tolerability of naloxegol when used for the treatment of OIC.

Exploratory objectives

The exploratory objectives were to characterize the PK of naloxegol and the covariate effect in the targeted disease population, explore the naloxegol exposure-response relationship, collect and store deoxyribonucleic acid (DNA) for future exploratory research, assess patient health status index and healthcare resource utilization, and assess patients' willingness to take the study drug again.

Outcomes/endpoints

The primary efficacy endpoint was response (responder/non-responder) to study drug during Weeks 1 to 12. The endpoint incorporates both the durability of effect and a clinically relevant increase in the SBM rates across the 12-week treatment period.

The key secondary efficacy endpoints were chosen to further characterize SBM improvement in OIC patients. The key secondary efficacy endpoints are:

1. Response to study drug in the LIR subgroup during Weeks 1 to 12 - to examine efficacy in this particular subgroup, which is characterized by continued moderate to very severe OIC symptoms, despite laxative use.
2. Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 h - to examine speed of onset. This end point is relevant given that many patients may want to have prompt relief of symptoms and be able to predict the onset of action.
3. Mean number of days per week with at least 1 SBM (and less than 4 SBMs/day) during Weeks 1 to 12 - to examine regularity of SBMs, ie, the degree to which the SBMs occur on separate days, as opposed to multiple SBMs on a small number of days.

The other secondary endpoints assessed to further characterize the efficacy of naloxegol are:

1. Response (responder/non-responder) to study drug during Weeks 1 to 4.
2. Response (responder/non-responder) to study drug in the LIR subgroup during Weeks 1 to 4.
3. Change from baseline in number of SBMs/week for Weeks 1 to 4 and 1 to 12.
4. Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours in the LIR subgroup.
5. Response within the first 12 hours of treatment.
6. Mean number of days per week with at least 1 SBM for Weeks 1 to 4.
7. Change from baseline in the mean degree of straining for Weeks 1 to 4 and 1 to 12.
8. Change from baseline in the mean stool consistency (BSS) for Weeks 1 to 4 and 1 to 12.
9. Percentage of days with CSBM for Weeks 1 to 4 and 1 to 12.
10. Mean bisacodyl dose per week for Weeks 1 to 4 and 1 to 12.
11. Change from baseline in PAC-SYM total score (to assess symptoms of constipation)and each domain score for Weeks 2, 4, 8, and 12.
12. Change from baseline in PAC-QOL total score (to assess disease-specific quality of life) and each domain score for Weeks 4 and 12.

Safety endpoints

1. Adverse events (ie, incidence, nature, and intensity of AEs, treatment-related AEs, SAEs, AEs leading to discontinuation, and AEs of special interest).
2. Change from baseline in the mean daily opioid dose for Weeks 1 to 4 and 1 to 12.
3. Change from baseline in the mean NRS pain score for Weeks 1 to 4 and 1 to 12.
4. Observed values and change from baseline in composite score in modified Himmelsbach scale (mHS) for the evaluation of centrally mediated opioid withdrawal symptoms 2 hours after first dose of study drug, and at Weeks 1, 4, and 12.
5. Changes in vital signs, weight and BMI, and changes in physical examination.
6. Changes in laboratory assessments (ie, chemistry, hematology, and urinalysis).
7. Changes in ECGs.
8. Occurrence of suicidal behaviour/suicidal ideation throughout the study based on the C-SSRS.

Exploratory

- Population PK modelling work.
- Exposure/ response modelling work.
- Data on the EQ-5D questionnaire for Weeks 4 and 12.
- Data on OIC healthcare resource utilization captured at the site for economic modelling purposes.

Health

Economic

Willingness to Take Drug Again questionnaire for Week 12.

DNA extracted from the optional blood samples may be used to explore relationships between genetic variability and NKTR-118 PK/PD, safety, tolerability, response, and OIC.

Sample size

A sample size of 105 patients per group would have been needed to detect a difference of 25% in response rate (60% on NKTR-118 and 35% on placebo), with power=90%, alpha=0.025, and 2-sided test. In order to provide an adequate power to detect a treatment difference in LIR subgroup (assuming LIR is 50% of the total study population), it was recommended that 210 patients per group (total 630 patients for 3 treatment groups) be randomized to the study. The assumptions on expected response rate were referenced from the NKTR-118 Phase II study and from other similar drugs based on response over 4 weeks. It was assumed that a similar magnitude in relative treatment effect would hold for the response assessed over 12 weeks.

Randomisation

Randomization occurred at the onset of the 12-week, double-blind treatment period at Visit 3. Patients were stratified based on their response to laxative use (LIR, LAR, LUR), and were randomly assigned in a 1:1:1 ratio (approximately 210 patients per treatment group) to receive placebo, or naloxegol at a dose of 12.5 or 25 mg once daily (QD), with a minimum of 50% of patients randomized in the LIR category.

Blinding (masking)

The study was conducted in a double-blind manner. Naloxegol 12.5 and 25 mg tablets were identical in size and colour to their respective placebo tablets. Packaging and labelling of the investigational products (IPs) were performed in a way to ensure blinding throughout the study. Patients received 2 tablets per dose, irrespective of which randomized dose they receive.

No member of the study team or company representative, at investigational centres or any contract research organization (CRO) handling data had access to the randomization scheme during the conduct of the study with the exception of the company's Research and Development Supply Chain.

The randomization schedule for blinding of randomized treatment was maintained by the company and was not to be disclosed until after database lock.

Statistical methods

The efficacy analyses utilized the ITT Analysis Set, consisting of all patients randomized to study treatment for the duration of their participation in the confirmatory studies. A decision was made and documented prior to database lock, to exclude patients from the ITT analysis set who had previously or concurrently participated in the naloxegol program at another study centre. All data were retained in the database and included in the patient data listings in the CSRs.

Results were summarized using frequency and percentages for categorical data and n, mean, standard deviation, median, minimum, maximum for continuous data. Treatment comparisons were made between each active treatment group (NKTR-118 12.5 mg and 25 mg) vs placebo for all data analyzed. The primary endpoint, response over 12 weeks, was analyzed using Cochran-Mantel-Haenszel (CMH) tests stratified by response to laxatives at baseline (LIR, laxative adequate responder [LAR], laxative unknown responder [LUR]). The treatment effect was further characterized by the relative risk (RR, NKTR-118/placebo) with associated 2-sided 95% confidence intervals (CIs).

To control the overall Type I error rate to be < 0.05 for the multiple pairwise comparisons versus placebo in the primary and the key secondary endpoints, an MTP with Bonferroni- Holm over dose groups, and fixed-sequence within groups (in the order below) was applied:

- 12-week responder analysis in the ITT analysis set (primary endpoint, analyzed via the Cochran Mantel Haenszel test stratified by baseline laxative response),

- Comparison of the response rate of Weeks 1 to 12 of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo in the LIR subgroup. Difference between treatment groups in response rate was analyzed using Chi-Square tests. The treatment effect was characterized by the RR (NKTR-118 group/placebo) with associated 2-sided 95% CIs.

- Treatment comparisons of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo, for the time to first laxation without laxative use in the previous 24 hours were analyzed using log rank tests stratified by response to laxatives at baseline (LIR, LAR, LUR).

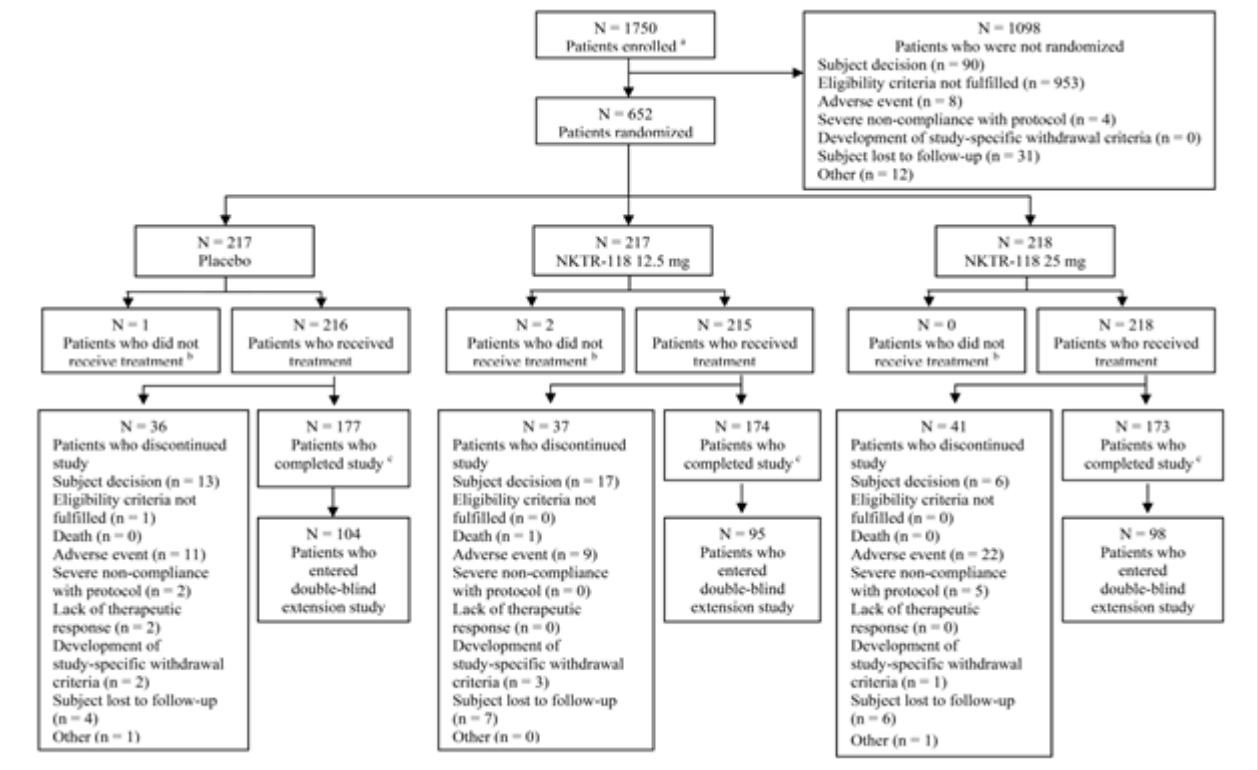
- Comparison of the mean number of days per week with at least 1 SBM during the 12 weeks of treatment of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo (analyzed via Mixed Model Repeated Measures [MMRM]).

All continuous efficacy endpoints were analyzed formally via a MMRM approach. MMRM models adjusted for fixed effects of treatment, baseline value, week, treatment-by-week interaction, baseline laxative responder status with center and patient incorporated via random effects.

Endpoints for daily symptoms, Patient Assessment of Constipation Symptoms (PAC-SYM), Patient Assessment of Constipation Quality of Life (PAC-QOL), morphine equivalent dose, and Numeric Rating Scale (NRS) pain score, were analyzed using a mixed model repeated measures approach in a similar manner to that described above.

Results

Participant flow



Recruitment

Recruitment started in July 2011 and ended in September 2012. Both male and female patients, between 18 and 84 years of age, have been enrolled in the study in United States, Australia, Germany and Slovakia.

C**onduct of the study**

Of the 138 study centres selected for this study, 115 screened at least 1 patient and 98 randomized patients into the study. This study was conducted in the following countries: Australia (1 centre), Germany (5 centres), Slovakia (4 centres), and the United States (US) (88 centres). Time of clinical part: from 14 March 2011 (first subject enrolled), to 16 August 2012 (last subject last visit).

The original study protocol date was 01 December 2010. There were 2 global amendments (17 February 2011 and 02 November 2011). The Company's Clinical Study Team was responsible for all amendments and changes to the study conduct. All protocol amendments were approved by the company before being submitted to a regulatory authority and/or an EC/IRB. The implementation of the protocol amendments

did not have a significant effect on the composition of the study population or the interpretation of the study results.

Baseline data

Study 04 enrolled an OIC population representative of patients receiving long-term opioid treatment for non-cancer pain, with respect to demographic and baseline disease characteristics.

In general, baseline demographic data were similar across treatment groups. Most patients randomized in this study were White (497 patients; 77.5%), and the mean age of patients was 52.3 years of age. The percentage of participating females was higher than males, and 331 (51.6%) patients had a BMI ≥30 kg/m2. There were slightly more males included in the NKTR-118 25 mg group than in the NKTR-118 12.5 mg or placebo treatment groups. Overall, the mean BMI was similar across treatment groups: 31.6, 32.1, and 31.3 kg/m2 in the NKTR-118 25 mg, 12.5 mg, and placebo groups, respectively.

Patients were required to have an opioid-requiring pain condition and to be receiving a stable maintenance opioid regimen.

The total opioid dose was calculated as the sum of the maintenance and breakthrough opioid use. At baseline there were no notable imbalances between treatment groups in mean daily morphine equivalent dose: means were 143.2 mg/day, 139.7 mg/day, 135.6 mg/day in the NKTR-118 25 mg, NKTR-118 12.5 mg, and placebo groups, respectively. The most commonly used maintenance opioid medications were hydrocodone + paracetamol (176 patients; 27.5%), morphine (157 patients; 24.5%), and oxycodone (154 patients; 24.0%). On average, the distribution of maintenance opioid medications was similar across treatment groups.

The most frequent main complaints with constipation were straining (146 patients; 22.8%), infrequent defecation (133 patients; 20.7%), hard stools (97 patients; 15.1%), and abdominal pain (91 patients; 14.2%). More patients had experienced abdominal pain since the start of their current opioid treatment than had not: 380 patients (59.3%) compared with 258 patients (40.2%). Overall, for the majority of patients, the location of abdominal pain was in the right or left lower quadrant: 257 (40.1%) and 267 (41.7%) patients, respectively; and was intermittent rather than constant: 327 (51.0%) compared with 53 (8.3%) patients, respectively.

Numbers analysed

A total of 1750 patients were enrolled in the study and of these, 652 patients completed the OIC confirmation period, were randomized, and entered the double-blind treatment period. Of the randomized patients, 99.5% received treatment, 80.4% completed the study (defined as completing Visit 8 [Week 12] for patients who continued into the safety extension study, or completing Visit 9 [Week 14] for patients who did not continue into the safety extension study), and 17.5% received treatment and subsequently discontinued the study. Of the 652 randomized patients, 297 (45.6%) who were included in the intent-to-treat (ITT) analysis set completed the study and continued into the double-blind safety extension study (D3820C00007). A total of 11 additional patients completed the study, but had previously or concurrently participated in the NKTR-118 program at another study centre and were excluded from the ITT and safety analysis sets. Of the 652 patients randomised, 17.5% discontinued the study: 18.8%, 17.1%, and 16.6% in the NKTR-118 25 mg, 12.5 mg, and placebo groups, respectively. The most common reasons for study withdrawal were adverse events (AEs) (6.4%) and subject decision (5.5%). The proportion of patients who discontinued treatment due to AEs was higher in the NKTR-118 25 mg treatment group (10.1%) than in the 12.5 mg (4.1%) or placebo (5.1%) treatment groups. Overall, there were no imbalances across the treatment groups in terms of patient characteristics that could have a potential influence on the results and their interpretation. Treatment groups were generally balanced

across analysis sets with respect to: disposition; protocol deviations; demographic and baseline characteristics; prior and concomitant medications, including the pattern of laxative classes taken prior to study entry, satisfaction with laxative classes, and the pattern of related severity of symptoms; and treatment compliance. Most patients were taking laxatives prior to enrolment into the study. The US was the predominant region accounting for most randomized patients. The patient population recruited to the study was considered representative of OIC patients globally with respect to demographic and disease characteristics at baseline.

Outcomes and estimation

The *primary efficacy variable* is the response (responder/non-responder) to study drug during Weeks 1 to 12. A SBM was defined as a BM without the use of rescue laxatives (bisacodyl or enema) administered in the previous 24 hours. A responder to study drug during Weeks 1 to 12 was defined as a patient with at least 3 SBMs/week and at least a 1 SBM/week increase over baseline for at least 9 out of the 12 treatment weeks and 3 out of the last 4 treatment weeks during the double-blind treatment period demonstrated by the primary analysis in the ITT analysis set.

Cochran Mantel-Haenszel analysis of response rate for Weeks 1 to 12 (Intent-to-treat analysis set)					
Treatment Group	n	Number (%) of patients responding	Comparison versus Placebo		
			RR	95% CI	p-value
Placebo	214	63 (29.4)	NA	NA	NA
NKTR-118 12.5 mg	213	87 (40.8)	1.380	(1.062, 1.795)	0.015 *
NKTR-118 25 mg	214	95 (44.4)	1.509	(1.168, 1.949)	0.001 *

* Statistically significant under the multiple testing procedure.

Statistically significant higher response rates were observed in the NKTR-118 25 mg and 12.5 mg treatment groups compared with placebo over 12 weeks in patients with OIC (p=0.001 and 0.015, respectively). The response rate at Week 12 was 15.0 percentage points and 11.4 percentage points higher, respectively, in the NKTR-118 25 mg and 12.5 mg groups, compared with placebo.

The following results were obtained for the *key secondary endpoints*:

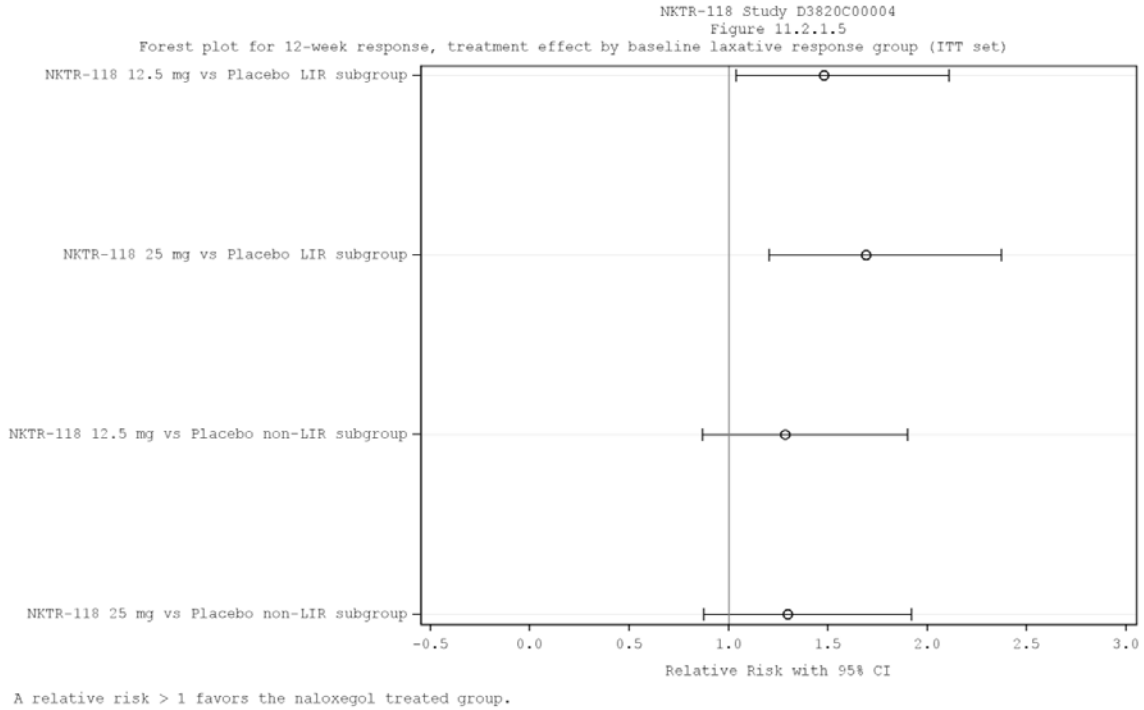
In the LIR subgroup, there was a statistically significantly higher response rate in the NKTR-118 25 mg (p=0.002) and 12.5 mg (p=0.028) groups compared with placebo over 12 weeks in patients with OIC. The response rate at Week 12 was 19.9 percentage points and 13.8 percentage points higher, respectively, in the NKTR-118 25 mg and 12.5 mg groups, compared with placebo. The RR estimates indicated that LIR subgroup patients in the NKTR-118 25 mg and 12.5 mg groups were 69.1% and 47.9%, respectively, more likely to respond than those randomized to placebo.

Analysis of response rate for Weeks 1 to 12 in the LIR subgroup (Intent-to-treat analysis set)					
Treatment Group	n	Number (%) of patients responding	Comparison versus Placebo		
			RR	95% CI	p-value
Placebo	118	34 (28.8)	NA	NA	NA
NKTR-118 12.5 mg	115	49 (42.6)	1.479	(1.038, 2.107)	0.028 *
NKTR-118 25 mg	117	57 (48.7)	1.691	(1.205, 2.373)	0.002 *

* Statistically significant under the multiple testing procedure.

It is important to note that in the non-LIR subgroup the effect of both doses of NKTR-118 (although formal statistical analysis was not performed) was not significant. The statistical analysis was made for the

pooled population (study 4 and study 5, see additional analyses). The forest plot for 12 week response (study 04 population) is presented below:



The time to first post-dose laxation was statistically significantly shorter for both the NKTR-118 25 mg and 12.5 mg treatment groups compared with placebo ($p<0.001$ for both comparisons). The NKTR-118 25 mg and 12.5 mg groups had shorter median time to first post-dose laxation compared with placebo (5.9, 20.4, and 35.8 hours, respectively). This was reflected by the proportions of patients who had a SBM by 6 hours (50.9%, 33.8%, and 15.4%, respectively), 12 hours (57.0%, 43.7%, and 22.9%, respectively), or 24 hours (70.1%, 58.7%, and 36.9%, respectively) in the 3 groups.

Time in hours to first post-dose SBM (Intent-to-treat analysis set)			
	Number (%) of patients		
	Placebo	**NKTR-118 12.5 mg**	**NKTR-118 25 mg**
	(N = 214)	**(N = 213)**	**(N = 214)**
Median time to first SBM a (hours)	35.8	20.4	5.9
(95% CI)	(27.0, 48.1)	(11.5, 22.7)	(4.8, 11.5)
Patient with SBM by ≤6 hours (%)	33 (15.4)	72 (33.8)	109 (50.9)
Patient with SBM by ≤12 hours (%)	49 (22.9)	93 (43.7)	122 (57.0)
Patient with SBM by ≤24 hours (%)	79 (36.9)	125 (58.7)	150 (70.1)

There was a statistically significant increase in the mean number of days per week with at least 1 SBM over Weeks 1-12 in the NKTR-118 25 mg and 12.5 mg treatment groups compared with placebo: 0.82; 95% CI (0.51, 1.13); $p<0.001$ and 0.55; 95% CI (0.24, 0.86); $p<0.001$, respectively.

Repeated measures analysis of change from baseline in mean number of days per week with at least 1 SBM (Intent-to-treat analysis set)						
Time point	**Treatment Group**	**n**	**LS Means (SEM)**	**Difference versus Placebo**		
				LS Mean	**95% CI**	**p-value**
Weeks 1 to 12	Placebo	211	1.66 (0.13)	NA	NA	NA
	NKTR-118 12.5 mg	211	2.21 (0.13)	0.55	(0.24, 0.86)	<0.001
	NKTR-118 25 mg	212	2.48 (0.13)	0.82	(0.51, 1.13)	<0.001
Baseline value used to calculate LS Means=1.30. Mean number of days per week with at least 1 SBM is a key secondary endpoint included in the multiple testing procedure. All patients with evaluable data at both baseline and at least 1 post-baseline week are included in the analysis.						

Degree of straining

At baseline, the 3 groups were comparable in mean degree of straining (3.2, 3.1, 3.3 in the 25 mg, 12.5 mg, and placebo groups, respectively). The mean straining scores across the treatment groups at baseline indicated a moderate level of straining. Over Weeks 1 to 12, there was a decrease in straining observed in all treatment groups, with larger decreases in the MMRM-estimated Least-Squares Mean changes from baseline (standard error of the mean [SEM]) of greater than 0.5 points seen with increasing doses of NKTR-118 (-0.73 [0.05], -0.64 [0.05], and -0.54 [0.05] for the 25 mg, 12.5 mg, and placebo groups, respectively). The 25 mg group showed an improvement in intensity of straining compared with placebo of -0.18 (p=0.008), while the 12.5 mg group showed a similar improvement in intensity of straining as that observed with placebo (non-significant difference) (p=0.176).

Stool Consistency (BSS ratings)

At baseline, the 3 groups were comparable in mean stool consistency assessed by BSS ratings (2.9, 2.9, 2.8 in the 25 mg, 12.5 mg, and placebo groups, respectively. The mean BSS scores across the treatment groups indicated relatively low symptom burden from stool hardness at baseline. BSS types 3 and 4 are considered to reflect "ideal stools." Over Weeks 1 to 12, the MMRM-estimated Least-Squares Means (SEM) indicated an increase in stool consistency in all treatment groups, with greater increases seen with increased doses of NKTR-118: 0.66 (0.07), 0.53 (0.07), and 0.47 (0.07) for the 25 mg, 12.5 mg, and placebo groups, respectively. The 25 mg group showed an improvement in BSS ratings compared with placebo of 0.18 (p=0.042), while the 12.5 mg group showed a similar improvement in BSS ratings as that observed with placebo (non-significant difference) (p=0.564).

Completeness of evacuation (percent number of days with a CSBM)

At baseline, the 3 groups were comparable in completeness of evacuation assessed by percent number of days per week with a CSBM (5.4, 6.5, 6.0 in the 25 mg, 12.5 mg, and placebo groups, respectively). Over Weeks 1 to 12, the MMRM-estimated Least-Squares Means (SEM) were 27.04 (1.75), 22.31 (1.73), and 18.45 (1.72) for the 25 mg, 12.5 mg, and placebo groups, respectively. The 25 mg group showed an increase in percent number of days with a CSBM/week compared with placebo of 8.59 (p<0.001). The 12.5 mg group showed a smaller increase in percent number of days with a CSBM/week compared with placebo of 3.87 (p=0.094).

Change from baseline in mean spontaneous bowel movements/week

There was an increase in mean SBMs per week in the NKTR-118 25 mg and 12.5 mg groups compared with placebo (0.99; p<0.001, and 0.54; p=0.011, respectively). These numbers correspond to approximately 4.4 SBMs per week in the NKTR-118 25 mg group compared with 3.9 and 3.4 SBMs per week in the NKTR-118 12.5 mg and placebo groups, respectively.

Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours in the LIR subgroup

In the LIR subgroup, the NKTR-118 25 mg and 12.5 mg groups had shorter median time to first post-dose laxation compared with placebo (5.4, 20.6, 43.4 hours, respectively)

The time to first post-dose laxation was significantly shorter for both the NKTR-118 25 mg and NKTR-118 12.5 mg groups compared with placebo ($p<0.001$ and $p=0.002$, respectively).

Predictability of response to study drug based on the first 12 hours

For the single analysis conducted to assess short- and long-term response relationship, there was no clear relationship between response in the first 12 hours and response over 12 weeks for the NKTR-118 25 mg group ($p=0.430$). In the NKTR-118 12.5 mg and placebo groups, patients who had a SBM within the first 12 hours were more likely to be considered responders over 12 weeks compared with patients who did not have an SBM within 12 hours ($p<0.001$ and $p=0.007$, respectively).

Rescue medication use

Over the 12-week study period, the mean weekly bisacodyl dose was low: 5.8 mg, 5.9 mg, and 10.3 mg in the NKTR-118 25 mg, 12.5 mg, and placebo groups, respectively. Over the 12-week study period, the median number of times that patients used bisacodyl as a rescue laxative was 1.0 for the NKTR-118 25 mg group, 2.0 for the NKTR-118 12.5 group, and 4.0 for placebo. The proportion of patients who used bisacodyl at least once was lower in the NKTR-118 25 mg (117 patients; 54.7%) and 12.5 mg (135 patients; 63.4%) groups compared with the placebo group (154 patients; 72.0%). No formal statistical analysis was conducted for this measure. Bisacodyl rescue medication usage during the first 4 weeks was similar to bisacodyl rescue medication usage over the 12-week period. The number and percentage of patients that used an enema 1 time or more than once during the study was low in the ITT analysis set and similar across treatment groups.

PAC-SYM assessment

A negative change from baseline using PAC-SYM indicates improvement. Scoring on the PAC-SYM ranged from 0 (absence of symptoms) to 4 (very severe) for each item. At baseline, the treatment groups were similar in PAC-SYM total score and abdominal, rectal, and stool domain scores. The mean baseline domain scores across all 3 treatment groups indicates that patients in the study were most affected by symptoms in the stool domain (moderate to severe) and affected to a lesser extent by symptoms in the abdominal and rectal domains (mild to moderate). Changes from baseline in the severity of constipation symptoms, as measured by PAC-SYM total score, rectal symptoms subscore and stool symptoms subscore at Week 12, were numerically greater for the NKTR-118 12.5 mg and 25 mg groups compared with placebo, however there are no statistically significant differences between analyzed groups (beside rectal symptoms subscore).

Change from baseline in PAC-QOL

A negative change from baseline using PAC-QOL indicates improvement. Changes from baseline in the satisfaction domain were of particular interest in this study and pre-defined for statistical analysis.

Compliance with the PAC-QOL was similar across treatment groups over study visits, ranging from 91% to 99% at individual visits.

At baseline, the treatment groups were similar in PAC-QOL total score and satisfaction, physical discomfort, psychosocial discomfort, and worries and concerns domain scores. All 3 treatment groups had negative changes from baseline to each visit in PAC-QOL total and all domain scores, indicating

improvement in quality of life for all patients. Changes from baseline in total score, physical discomfort, psychosocial discomfort, and worries and concerns domains for the NKTR-118 25 mg and 12.5 mg were comparable with placebo, and were not formally analyzed. The only significant effect was observed in NKTR-118 25 mg group in comparison to placebo group at Week 4 (p=0.002) in satisfaction domain but that effect disappeared at Week 12.

Summary of main efficacy results

The following table summarise the efficacy results from the main study D3820C00004 supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 6 Summary of efficacy for trial D3820C00004 (NCT01309841)

Title: Assessment of Efficacy and Safety in Patients With Non-cancer-related Pain and Opioid-induced Constipation			
Study identifier	D3820C00004 - NCT01309841 – 2011-001987-24		
Design	Phase III, multi-center, double-blind, randomized, placebo-controlled, parallel group study of 2 doses of NKTR-118 (25 mg and 12.5 mg) and placebo		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks 2 weeks 2 weeks
Hypothesis	Superiority		
Treatments groups	Placebo		Placebo treatment – 12 weeks – n=217
	Naloxegol 25 mg daily (NAL25)		25 mg naloxegol daily – 12 weeks – n=217
	Naloxegol 12.5 mg daily (NAL12,5)		12,5 mg naloxegol daily – 12 weeks – n=218
Endpoints and definitions	Primary efficacy endpoint	PE	Response (responder/non-responder) to study drug during Weeks 1 to 12, where a responder is defined as having 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 out of the last 4 weeks.
	Key secondary efficacy endpoint 1	SE1	Response (responder/non-responder) to study drug in the LIR subgroup during Weeks 1 to 12, where a responder is defined as having 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 out of the last 4 weeks.
	Key secondary endpoint 2	SE2	Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours.
	Key secondary endpoint 3	SE3	Mean number of days per week with at least 1 SBM during Weeks 1 to 12.
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat Timepoint: 12 week treatment period		

Descriptive statistics and estimate variability	Treatment group	Placebo	NAL12,5	NAL25
	Number of subjects	214	213	214
	PE	29.4%	40.8%	44.4%
	Treatment group	Placebo LIR subgroup	NAL12,5 LIR subgroup	NAL25 LIR subgroup
	Number of subjects	118	115	117
	SE1	28.8%	42.6%	48.7%
	Treatment group	Placebo	NAL12,5	NAL25
	Number of subjects	214	213	214
	SE2 (median time to first SBM (h))	35.8	20.4	5.9
	95% CI	(27.0,48.1)	(11.5,22.7)	(4.8,11.5)
	Number of subjects	211	211	212
	SE3 (mean)	1.66	2.21	2.48
	SEM	0.13	0.13	0.13

Effect estimate per comparison	PE	Comparison groups	Placebo – NAL12,5
		RR	1.380
		95% CI	(1.062,1.795)
		P-value (CMH test stratified to laxative response status at baseline)	0.015
	PE	Comparison groups	Placebo – NAL25
		RR	1.509
		95% CI	(1.168,1.949)
		P-value (CMH test stratified to laxative response status at baseline)	0.001
	SE1	Comparison groups	Placebo – NAL12,5 LIR subgroup
		RR	1.479
		95% CI	(1.038,2.107)
		P-value	0.028
	SE1	Comparison groups	Placebo – NAL25 LIR subgroup
		RR	1.691
		95% CI	(1.205,2.373)
		P-value	0.002

Notes	The effect sizes for the PE endpoint and first key secondary endpoint response rate were not reported as RR with 95% CI. The 25% effect size in response rate (treatment versus placebo) based on the response over 4 weeks from the Phase 2b study, for which the phase 3 study was designed, was not demonstrated by the primary endpoint nor the first key secondary endpoint based on response over 12 weeks.

STUDY 05 (Study code D3820C00005)

This was a Phase III, multi-centre, double-blind, randomized, placebo-controlled, parallel group study of 2 doses of NKTR-118 (25 mg and 12.5 mg) and placebo. The study duration was up to 18 weeks, consisting of an initial screening period lasting up to 2 weeks, a 2-week OIC confirmation period, during which the diagnosis of OIC and stability of the opioid regimen were confirmed, a 12-week treatment period, and a follow-up visit 2 weeks after the last dose of study drug.

Methods

Study Participants

Adult patients who were receiving a stable maintenance opioid regimen (total daily dose of 30 to 1000 mg of oral morphine, or equianalgesic amount[s] of 1 or more other opioid therapies for a minimum of 4 weeks) for non-cancer-related pain and who reported a history of <3 spontaneous bowel movements (SBMs)/week and at least 1 OIC associated symptom at screening and had a confirmed diagnosis of OIC were eligible to be randomized.

Confirmed OIC was defined as: documented <3 SBMs/week on average over the 2-week OIC confirmation period. In addition to the SBM frequency criterion, patients must have reported ≥1 of the following symptoms in at least 25% of the bowel movements (BMs) recorded in the electronic diary during the OIC confirmation period Bristol Stool Scale stool type 1 or 2; moderate, severe, or very severe straining; incomplete BM.

In addition, a minimum of 50% of patients were to meet the following criteria for being laxative inadequate responders (LIR): Patient must have been taking 1 laxative class for a minimum of 4 days over the 14 days prior to the screening visit and report moderate, severe, or very severe symptoms in at least 1 of the 4 stool symptom domains to qualify for assessment of LIR.

Main inclusion criteria

The studies enrolled adult patients who were between the ages of ≥18 and <85 years:

- whose OIC diagnosis had been confirmed prospectively with a 2 week daily diary;
- who were receiving a stable maintenance opioid regimen for a minimum of 4 weeks for non-cancer-related pain;
- and who reported a history of <3 SBMs/week and at least 1 OIC-associated symptom at screening and had a confirmed diagnosis of OIC.

Main exclusion criteria

Patients presenting any of the following conditions were not included in the trial:

- patients with pre-existing constipation for reasons other than opioid treatment, or patients who had diarrhea;
- patients with potentially weakened integrity of the GI wall, due to risk for bowel perforation;
- patients who required concomitant prohibited medication (ie, strong inhibitors of CYP3A4 or P-gp, opioid antagonists and mixed agonists/antagonists, and laxatives);
- patients with potential for blood-brain barrier disruptions (eg, active multiple sclerosis, recent brain injury, advanced Alzheimer's disease, uncontrolled epilepsy);
- patients with cancer pain;
- and patients with recent history of myocardial infarction (MI), symptomatic congestive heart failure, or any other overt CV disease.

Treatments

NKTR-118 12.5 mg or 25 mg tablets, or matching placebo, administered once daily. The duration of treatment was 12 weeks. Study drug tablets were round, biconvex, and white film coated. Tablets were supplied in high-density polyethylene (HDPE) bottles, dispensed every 30 days. Each 30-day supply consisted of 2 bottles of study drug, each containing 35 tablets.

Objectives

Primary objectives

The primary objective of this study was to compare the efficacy of NKTR-118 12.5 mg and 25 mg with placebo in the treatment of patients who have OIC.

Secondary objectives

The secondary objectives were to compare NKTR-118 12.5 mg and 25 mg with placebo on the daily signs and symptoms associated with OIC (straining, sensation of incomplete evacuation, and stool consistency), symptoms of constipation, and quality of life.

Safety objective

The safety objectives were to assess the safety and tolerability of NKTR-118 when used for the treatment of OIC.

Exploratory objectives

The exploratory objectives were to characterize the PK of NKTR-118 and the covariate effect in the targeted disease population, explore the NKTR-118 exposure-response relationship, collect and store deoxyribonucleic acid (DNA) for future exploratory research, assess patient health status index and healthcare resource utilization, and assess patients' willingness to take the study drug again.

Outcomes/endpoints

Primary

Response (responder/non-responder) to study drug during Weeks 1 to 12.

Key Secondary

- Response (responder/non-responder) to study drug in the LIR subgroup during Weeks 1 to 12.
- Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours.
- Mean number of days per week with at least 1 SBM during Weeks 1 to 12.

Other Secondary

- Response (responder/non-responder) to study drug during Weeks 1 to 4.
- Response (responder/non-responder) to study drug in the LIR subgroup during Weeks 1 to 4.
- Change from baseline in number of SBMs/week for Weeks 1 to 4 and 1 to 12.
- Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours in the LIR subgroup.
- Response within the first 12 hours of treatment.
- Mean number of days per week with at least 1 SBM for Weeks 1 to 4.
- Change from baseline in the mean degree of straining for Weeks 1 to 4 and 1 to 12.
- Change from baseline in the mean stool consistency (BSS) for Weeks 1 to 4 and 1 to 12.
- Percentage of days with CSBM for Weeks 1 to 4 and 1 to 12.
- Mean bisacodyl dose per week for Weeks 1 to 4 and 1 to 12.
- Change from baseline in PAC-SYM total score and each domain score for Weeks 2, 4, 8, and 12.
- Change from baseline in PAC-QOL total score and each domain score for Weeks 4 and 12.

Safety

- Adverse events (ie, incidence, nature, and intensity of AEs, treatment-related AEs, SAEs, AEs leading to discontinuation, and AEs of special interest).
- Change from baseline in the mean daily opioid dose for Weeks 1 to 4 and 1 to 12.
- Change from baseline in the mean NRS pain score for Weeks 1 to 4 and 1 to 12.
- Observed values and change from baseline in composite score in mHS for the evaluation of centrally mediated opioid withdrawal symptoms 2 hours after first dose of study drug, and at Weeks 1, 4, and 12.
- Changes in vital signs, weight and BMI, and changes in physical examination.
- Changes in laboratory assessments (ie, chemistry, hematology, and urinalysis).
- Changes in ECGs.

- Occurrence of suicidal behaviour/suicidal ideation throughout the study based on the C-SSRS.

Exploratory

- Population PK modelling work.
- Exposure/ response modelling work.
- Data on the EQ-5D questionnaire for Weeks 4 and 12.
- Data on OIC healthcare resource utilization captured at the site for economic modelling purposes.

Health

Economic

Willingness to Take Drug Again questionnaire for Week 12.

DNA extracted from the optional blood samples may be used to explore relationships between genetic variability and NKTR-118 PK/PD, safety, tolerability, response, and OIC.

Sample size

A sample size of 105 patients per group would have been needed to detect a difference of 25% in response rate (60% on NKTR-118 and 35% on placebo), with power=90%, alpha=0.025, and 2-sided test. In order to provide an adequate power to detect a treatment difference in LIR subgroup (assuming LIR is 50% of the total study population), it was recommended that 210 patients per group (total 630 patients for 3 treatment groups) be randomized to the study. The assumptions on expected response rate were referenced from the NKTR-118 Phase II study and from other similar drugs based on response over 4 weeks. It was assumed that a similar magnitude in relative treatment effect would hold for the response assessed over 12 weeks.

Randomisation

Randomization occurred at the onset of the 12-week, double-blind treatment period at Visit 3. Patients were stratified based on their response to laxative use (LIR, LAR, LUR), and were randomly assigned in a 1:1:1 ratio (approximately 210 patients per treatment group) to receive placebo, or NKTR-118 at a dose of 12.5 or 25 mg once daily (QD), with a minimum of 50% of patients randomized in the LIR category.

Eligible patients will be randomized in balanced blocks to receive NKTR-118 12.5 mg, NKTR-118 25 mg, or matching placebo in a 1:1:1 ratio. The actual treatment given to individual patients will be determined by a randomization scheme that has been loaded into the IVRS database. The randomization scheme will be produced by a computer software program called GRand (Global Randomization system) that incorporates a standard procedure for generating random numbers. If a patient is discontinued from the study, his/her patient number or enrolment number will not be reused, and the patient will not be allowed to re-enter the study. Randomized patients who discontinue early from the study will not be replaced. Randomization codes will be assigned strictly sequentially within the response to laxative categories as patients become eligible for randomization.

If a randomization number is allocated incorrectly, no attempt should be made to remedy the error once the investigational product has been dispensed. The patient will continue with the allocated number and IP. AstraZeneca or its representative should be notified as soon as the error is discovered. Subsequent patients will continue using the first unallocated randomization number in the original numbering

sequence. Entry of incorrect stratification information into the IVRS will not disqualify a patient from continuation in the study.

Blinding (masking)

NKTR-118 12.5 and 25 mg tablets will be identical in size and colour to their respective placebo tablets. Packaging and labeling of the investigational products will be performed in a way to ensure blinding throughout the study. Patients will receive 2 tablets per dose, irrespective of which randomized dose they receive.

No member of the company's study team or its representative, at investigational centers or any contract research organization handling data will have access to the randomization scheme during the conduct of the study with the exception of company's Research and Development Supply Chain. The randomization schedule for blinding of randomized treatment will be maintained by the company and will not be disclosed until after database lock.

Statistical methods

The primary endpoint, response over 12 weeks, was analyzed using Cochran-Mantel-Haenszel (CMH) tests stratified by response to laxatives at baseline (LIR, laxative adequate responder [LAR], laxative unknown responder [LUR]). The treatment effect was further characterized by the relative risk (RR, NKTR-118/placebo) with associated 2-sided 95% confidence intervals (CIs).

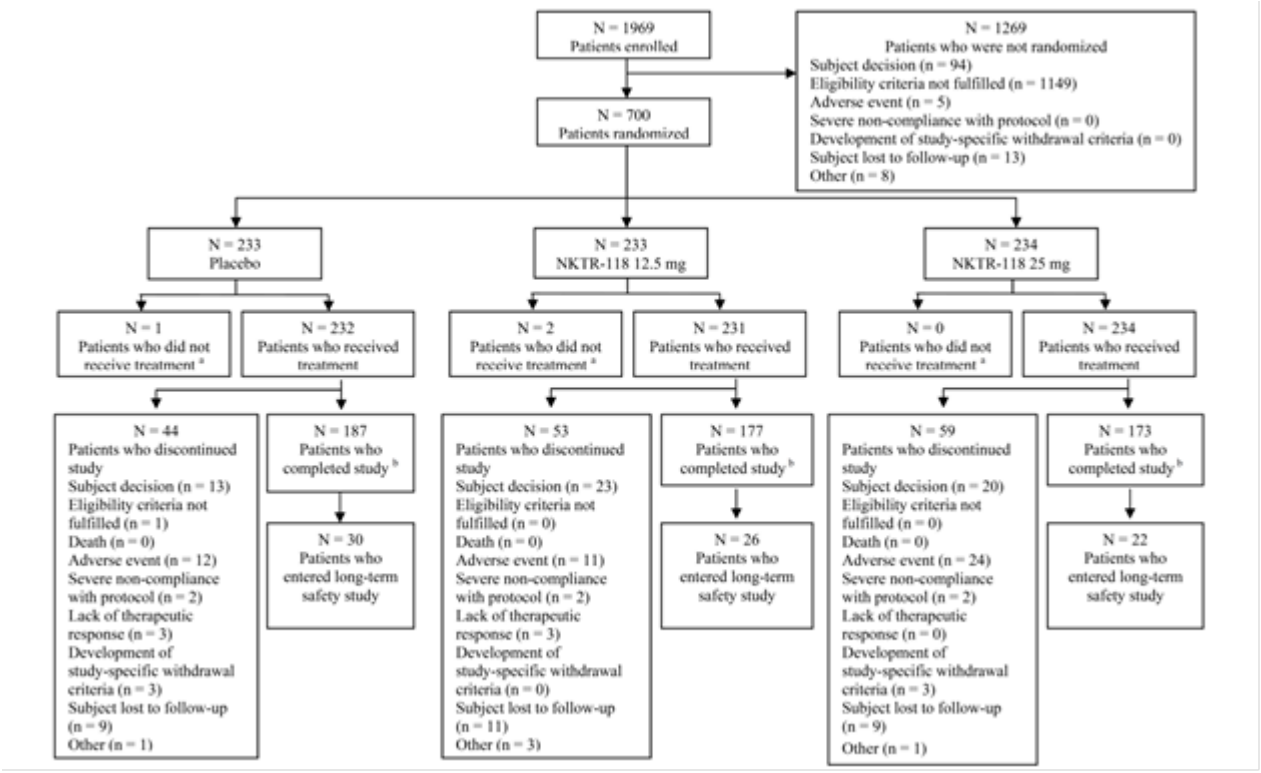
The following were categorized as key secondary endpoints and analyzed as indicated:

1. Comparison of the response rate of Weeks 1 to 12 of NKTR-118 12.5 mg vs. placebo and NKTR-118 25 mg vs. placebo in the LIR subgroup. Difference between treatment groups in response rate was analyzed using Chi-Square tests. The treatment effect was characterized by the RR (NKTR-118 group/placebo) with associated 2-sided 95% CIs.
2. Treatment comparisons of NKTR-118 12.5 mg vs. placebo and NKTR-118 25 mg vs placebo, for the time to first laxation without laxative use in the previous 24 hours were analyzed using log rank tests stratified by response to laxatives at baseline (LIR, LAR, LUR).
3. Comparison of the mean number of days per week with at least 1 SBM during the 12 weeks of treatment of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. Differences between treatment groups were analyzed using a mixed model for repeated measures. The model included factors for treatment, baseline laxative response status, time (Weeks 1 through 12 as a categorical variable), mean baseline value and treatment-by-time interaction as fixed effects, and center as a random effect. Descriptive statistics for the mean number of days per week with at least 1 SBM over Weeks 1 to 12 were also presented by treatment group. To control the overall type I error rate to be ≤ 0.05 for the multiple comparisons in the primary and the key secondary endpoints, a Multiple Testing Procedure with Bonferroni-Holm over groups, and fixed-sequence within groups was applied, with the endpoints tested in the order indicated above.

Endpoints for daily symptoms, Patient Assessment of Constipation Symptoms (PAC-SYM), Patient Assessment of Constipation Quality of Life (PAC-QOL), morphine equivalent dose, and Numeric Rating Scale (NRS) pain score, were analyzed using a mixed model repeated measures approach in a similar manner to that described above.

Results

Participant flow



A total of 1969 patients entered screening.

A total of 700 patients completed the OIC confirmation period, were randomized, and entered the double-blind treatment period. Of these patients, 697 (99.6%) received treatment, and 537 (76.7%) completed the study (defined as completing Visit 8 [Week 12] for patients who continued into the long-term safety study, or completing Visit 9 [Week 14] for patients who did not continue into the long-term safety study). Patients who did not enter the long-term safety study were to participate in a follow-up visit 2 weeks after the last dose of study drug.

Overall, 78 patients from the ITT analysis set (11.1% of the total randomized) completed the study and continued into long-term safety study D3820C00008.

A total of 4 additional patients (2 patients in the NKTR-118 25 mg group and 1 patient each in the NKTR-118 12.5 mg and placebo groups) received treatment, but had previously or concurrently participated in the NKTR-118 program at another study center. Three of these patients (0.4%; 1 patient in each treatment group) completed the study. These 4 patients were identified prior to database lock and were not included in the ITT or Safety analysis sets (see Section 2.2 of the SAP in CSR Appendix 12.1.9). The remaining text in this section describes the patients in the ITT analysis set; however, percentages are based on the total number of patients randomized.

A total of 156 patients (22.3%) who received treatment discontinued the study. The most common reason for discontinuation from the study was subject decision (56 patients; 8.0% overall). The number and percentage of patients who were withdrawn due to subject decision was 20 (8.5%) in the NKTR-118 25 mg group, 23 (9.9 %) in the NKTR-118 12.5 mg group, and 13 (5.6%) in the placebo group. The second most common reason for discontinuation was AEs (47 patients; 6.7% overall). A greater

proportion of patients were withdrawn due to Aes in the NKTR-118 25 mg group (24 patients; 10.3%) compared with the NKTR-118 12.5 mg group (11 patients; 4.7%) and the placebo group (12 patients, 5.2%).

Information on patients who withdrew from the study was provided on the Withdrawal CRF pages, however information for discontinuation of IP due to AEs (DAEs) was derived from the "action taken regarding study drug" field of the AE CRF pages, resulting in discrepancies between these 2 CRF pages for 1 patient.

A total of 696 patients were randomized and included in the ITT analysis set at 117 centers in Belgium (7 patients; 1.0%), Croatia (8 patients; 1.1%), Czech Republic (10 patients; 1.4%), Hungary (14 patients; 2.0%), Spain (15 patients; 2.2%), Sweden (2 patients; 0.3%), United Kingdom (4 patients; 0.6%), and the US (636 patients; 91.4%).

Recruitment

Recruitment started in March 2011 and ended in September 2012. Both male and female patients, between 18 and 84 years of age, have been enrolled in the study in United States, Belgium, Croatia, Czech Republic, Hungary, Spain, Sweden and United Kingdom.

Conduct of the study

In Study 05, following incorrect allocation of the subject number to the eDiary device, diary data from 1 LUR patient (E5214029) randomized to the NKTR-118 25 mg treatment group was assessed to be non-retrievable when the database was locked initially. The patient was initially classified as a non-responder. The exclusion of this retrievable data was considered, following the company's standard operating procedures, to be a critical data error and as such the database was unlocked in order that the diary data from this patient could be included in the final analysis.

The final analysis was completed after the diary data for this patient was added to the database, and the database was re-locked. For the primary variable, the relative risk and corresponding p-value for the NKTR-118 25 mg group vs placebo were 1.33 and 0.026, respectively, following the initial database lock and 1.35 and 0.021, respectively, after the final database lock.

Baseline data

Overall, there were no notable imbalances across the treatment groups in terms of patient characteristics that could have a potential influence on the results and their interpretation. Treatment groups were generally balanced across analysis sets with respect to: disposition; protocol deviations; demographic and baseline characteristics; prior and concomitant medications, including the pattern of laxative classes taken prior to study entry, satisfaction with laxative classes, and the pattern of related severity of symptoms; and treatment compliance. Most patients were taking laxatives prior to enrolment into the study. The US was the predominant region accounting for most randomized patients. The patient population recruited to the study was considered representative of OIC patients globally with respect to demographic and disease characteristics at baseline.

Numbers analysed

A total of 1969 patients were enrolled in the study and of these, 700 patients completed the OIC confirmation period, were randomized, and entered the double-blind treatment period. Of the randomized

patients, 99.6% received treatment, 76.7% completed the study (defined as completing Visit 8 [Week 12] for patients who continued into the long-term safety study, or completing Visit 9 [Week 14] for patients who did not continue into the long-term safety study), and 22.3% received treatment and subsequently discontinued the study. Of the 700 randomized patients, 78 (11.1%) who were included in the intent-to-treat (ITT) analysis set completed the study and continued into the long-term safety study (D3820C00008).

A total of 3 additional patients completed the study, but had previously or concurrently participated in the NKTR-118 program at another study center and were excluded from the ITT and safety analysis sets.

Of the 700 patients randomised, 22.3% discontinued the study: 25.2%, 22.7%, and 18.9% in the NKTR-118 12.5 mg, 25 mg, and placebo groups, respectively.

The most common reasons for study withdrawal were subject decision (8.0%) and adverse events (AEs, 6.7%). A greater proportion of patients discontinued treatment due to AEs in the NKTR-118 25 mg group (10.3%) compared with the NKTR-118 12.5 mg group (4.7%) and the placebo group (5.2%).

Overall, there were no notable imbalances across the treatment groups in terms of patient characteristics that could have a potential influence on the results and their interpretation. Treatment groups were generally balanced across analysis sets with respect to: disposition; protocol deviations; demographic and baseline characteristics; prior and concomitant medications, including the pattern of laxative classes taken prior to study entry, satisfaction with laxative classes, and the pattern of related severity of symptoms; and treatment compliance. Most patients were taking laxatives prior to enrollment into the study. The US was the predominant region accounting for most randomized patients. The patient population recruited to the study was considered representative of OIC patients globally with respect to demographic and disease characteristics at baseline.

Outcomes and estimation

Primary variable: response (responder/non-responder) to study drug during Weeks 1 to 12

The primary efficacy variable is the response (responder/non-responder) to study drug during Weeks 1 to 12.

A SBM was defined as a BM without the use of rescue laxatives (bisacodyl or enema) administered in the previous 24 hours. A responder to study drug during Weeks 1 to 12 was defined as a patient with at least 3 SBMs/week and at least a 1 SBM/week increase over baseline for at least 9 out of the 12 treatment weeks and 3 out of the last 4 treatment weeks during the double-blind treatment period demonstrated by the primary analysis in the ITT analysis set. For the primary efficacy variable, there was a statistically significantly higher response rate in the NKTR-118 25 mg group ($p=0.021$) compared with placebo over 12 weeks in patients with OIC. There was no statistically significant difference between the 12.5 mg group and placebo ($p=0.202$). The response rate over 12 weeks was 10.4 percentage points and 5.6 percentage points higher, respectively, in the NKTR-118 25 mg and 12.5 mg groups, compared with placebo.

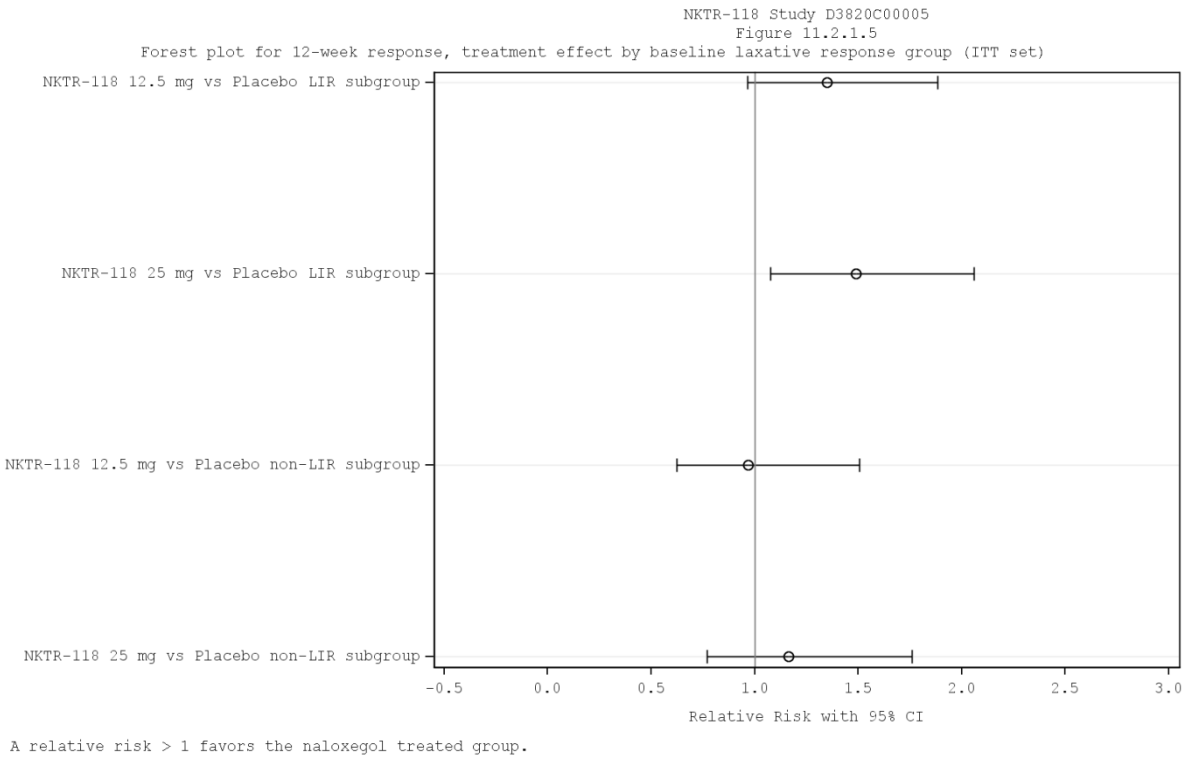
The RR estimates indicated that patients randomized to the NKTR-118 25 mg group were 34.8% more likely to respond than those randomized to placebo. The definition of the primary endpoint ensured that for a patient to be considered a responder, improvement in SBMs had to be durable over the 12-week treatment period.

Key secondary variables

Under the multiple testing procedure since the primary endpoint null hypothesis could not be rejected for the 12.5 mg dose versus placebo, statistical significance cannot be claimed for any key secondary endpoint in this dose group, although nominal unadjusted p-values are presented below.

In the LIR subgroup, there was a statistically significantly higher response rate in the NKTR-118 25 mg group (p=0.014) compared with placebo over 12 weeks in patients with OIC. There was no statistically significant difference between the 12.5 mg group and placebo (p=0.074). The response rate over 12 weeks was 15.4 percentage points and 11 percentage points higher, respectively, in the NKTR-118 25 mg and 12.5 mg groups, compared with placebo. The RR estimates indicated that LIR subgroup patients in the NKTR-118 25 mg and 12.5 mg groups were 48.9% and 35.0%, respectively, more likely to respond than those randomized to placebo.

It is important to note that in the non-LIR subgroup the effect of both doses of NKTR-118 (although formal statistical analysis was not performed) was not significant. The statistical analysis was made for the pooled population (study 4 and study 5, see additional analyses). The forest plot for 12 week response (study 05 population) is presented below:



The time to first post-dose laxation was significantly shorter for both the NKTR-118 25 mg and NKTR-118 12.5 mg groups compared with placebo (p<0.001 for both comparisons). The Kaplan-Meier curves for time to first post-dose SBM were similar for both the NKTR-118 12.5 mg and NKTR-118 25 mg groups. Under the multiple testing procedure, however, in the absence of a statistically significant difference for the 12.5 mg group compared with placebo on the primary endpoint, statistical significance cannot be claimed for this comparison.

The NKTR-118 25 mg and 12.5 mg groups had a shorter median time to first post-dose laxation compared with placebo (12.0, 19.3, 37.2 hours respectively). This was reflected by the proportions of patients who had a SBM by 6 hours (39.2%, 34.5%, and 17.2%, respectively), 12 hours (49.6%, 44.0%, and 24.6%, respectively), or 24 hours (61.2%, 58.6%, and 36.6%, respectively) in the 3 groups.

Mean number of days per week with at least 1 SBM during Weeks 1 to 12

Over Weeks 1 to 12, there was a statistically significant increase in mean number of days/week with at least 1 SBM compared to placebo in the NKTR-118 25 mg group (0.68; p<0.001). Over Weeks 1 to 12, there was an increase in mean number of days/week with at least 1 SBM in the NKTR-118 12.5 mg group compared to placebo (0.39; p=0.010), however this increase was not considered to be statistically significant when the multiple testing procedure was applied.

Other secondary variables

Degree of straining

At baseline, the 3 groups were comparable in mean degree of straining (3.2, 3.1, 3.3 in the 25 mg, 12.5 mg, and placebo groups, respectively). The mean straining scores across the treatment groups at baseline indicated a moderate level of straining. Over Weeks 1 to 12, there was a decrease in straining observed in all treatment groups, with larger decreases in the MMRM-estimated Least-Squares Mean changes from baseline (standard error of the mean [SEM]) of greater than 0.5 points seen with increasing doses of NKTR-118 (-0.80 [0.06], -0.67 [0.06], and -0.48 [0.06] for the 25 mg, 12.5 mg, and placebo groups, respectively). The 25 mg group showed an improvement in intensity of straining compared with placebo of -0.32 (p<0.001), while the 12.5 mg group showed an improvement in intensity of straining compared with placebo of -0.19 (p=0.005).

Stool Consistency (BSS ratings)

At baseline, the 3 groups were comparable in mean stool consistency assessed by BSS ratings (2.8, 3.0, 3.0 in the 25 mg, 12.5 mg, and placebo groups, respectively). Over Weeks 1 to 12, the MMRM-estimated Least-Squares Means (SEM) indicated an increase in stool consistency in all treatment groups, with greater increases seen with increased doses of NKTR-118: 0.71 (0.07), 0.54 (0.07), and 0.26 (0.06) for the 25 mg, 12.5 mg, and placebo groups, respectively. The 25 mg group showed an improvement in BSS ratings compared with placebo of 0.45 (p<0.001), while the 12.5 mg group showed an improvement in BSS ratings compared with placebo of 0.28 (p=0.001).

Completeness of evacuation (percent number of days with a CSBM)

At baseline, the 3 groups were comparable in completeness of evacuation assessed by percent number of days per week with a CSBM (5.4, 7.0, 6.0 in the 25 mg, 12.5 mg, and placebo groups, respectively). Over Weeks 1 to 12, the MMRM-estimated Least-Squares Means (SEM) were 27.20 (1.93), 23.48 (1.88), and 16.76 (1.86) for the 25 mg, 12.5 mg, and placebo groups, respectively.

The 25 mg group showed an increase in percent number of days with a CSBM/week compared with placebo of 10.43 (p<0.001). The 12.5 mg group showed an increase in percent number of days with a CSBM/week compared with placebo of 6.72 (p=0.002).

Analysis of the change from baseline in number of days per week with CSBM showed an increase in days with a CSBM of 1.90 days and 1.64 days for the 25 mg and 12.5 mg NKTR-118 groups, compared to 1.17 days for placebo (an improvement of 0.73 days and 0.47 days for the 25 mg and 12.5 mg groups versus placebo respectively). Results of the statistical analysis of days per week with at least 1 CSBM are equivalent to the statistical analysis of percent days per week with at least 1 CSBM.

Change from baseline in mean spontaneous bowel movements/week

There was an increase in mean SBMs per week in the NKTR-118 25 mg and 12.5 mg groups compared with placebo (1.04; p<0.001 and 0.52; p=0.028, respectively), and this increase was maintained over the entire 12-week treatment period. These numbers correspond to approximately 4.6 SBMs per week in the NKTR-118 25 mg group compared with 4.1 and 3.6 SBMs per week in the NKTR-118 12.5 mg and placebo groups, respectively.

Rescue medication use

Over the 12-week study period, the mean weekly bisacodyl dose was low: 6.6 mg, 6.1 mg, and 7.9 mg in the NKTR-118 25 mg, 12.5 mg and placebo groups, respectively. Over the 12-week study period, the median number of times that patients used bisacodyl as a rescue laxative was 1.0 for the NKTR-118 25 mg group, 1.0 for the NKTR-118 12.5 group, and 3.0 for placebo.

The proportion of patients who used bisacodyl at least once was lower in the NKTR-118 25 mg (133 patients; 57.3%) and 12.5 mg (133 patients; 57.3%) groups compared with the placebo group (164 patients; 70.7%). No formal statistical analysis was conducted for this measure. The number and percentage of patients that used an enema 1 time or more than once during the study was low in the ITT analysis set and similar across treatment groups.

Change from baseline in PAC-SYM

At baseline, the treatment groups were similar in PAC-SYM total score and abdominal, rectal, and stool domain scores. The mean baseline domain scores across all 3 treatment groups indicates that patients in the study were most affected by symptoms in the stool domain (moderate to severe) and affected to a lesser extent by symptoms in the abdominal and rectal domains (mild to moderate).

In all treatment groups, improvements compared to baseline were observed for each subscale. Differences between treatment groups in the PAC-SYM total score were primarily driven by differences in the rectal and stool subscales, with the abdominal symptoms sub-score comparable between treatment groups at all time points. For both the rectal and stool domains, improvements in scores compared with placebo were numerically greater for the NKTR-118 25 mg group compared with the 12.5 mg group, with the largest differences seen in the stool symptoms domain (-0.38, p<0.001 and -0.27, p=0.002) at 12 weeks.

Change from baseline in PAC-QOL

At baseline, the treatment groups were similar in PAC-QOL total score and satisfaction, physical discomfort, psychosocial discomfort, and worries and concerns domain scores. All 3 treatment groups had negative changes from baseline to each visit in PAC-QOL total and all domain scores, indicating improvement in quality of life for all patients.

The absolute value of changes from baseline in patient satisfaction as measured by the Satisfaction Domain of the PAC-QOL questionnaire were numerically greater for the NKTR-118 25 mg and 12.5 mg groups compared with the placebo group, in OIC patients in this study. Numerically greater differences were noted between the NKTR-118 25 mg group and the placebo group, and the NKTR-118 12.5 mg group and the placebo group, at both Week 4 (p<0.001 and p=0.015, respectively) and Week 12 (p<0.001 and p=0.011, respectively).

Changes from baseline in total score, physical discomfort, psychosocial discomfort, and worries and concerns domains for the NKTR-118 25 mg and 12.5 mg were comparable with placebo, and were not formally analyzed.

Summary of main efficacy results

Summary of main studies

The following table summarise the efficacy results from the main study D3820C00005 supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 7 Summary of efficacy for trial D3820C00005 (NCT01323790)

Title: Assessment of Efficacy and Safety in Patients With Non-cancer-related Pain and Opioid-induced Constipation					
Study identifier	D3820C00005 - NCT01323790 – 2011-001986-41				
Design	Phase III, multi-center, double-blind, randomized, placebo-controlled, parallel group study of 2 doses of NKTR-118 (25 mg and 12.5 mg) and placebo				
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks 2 weeks 2 weeks		
Hypothesis	Superiority				
Treatments groups	Placebo		Placebo treatment – 12 weeks – n=232		
	Naloxegol 25 mg daily (NAL25)		25 mg naloxegol daily – 12 weeks – n=231		
	Naloxegol 12.5 mg daily (NAL12,5)		12,5 mg naloxegol daily – 12 weeks – n=234		
Endpoints and definitions	Primary efficacy endpoint	PE	Response (responder/non-responder) to study drug during Weeks 1 to 12, where a responder is defined as having 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 out of the last 4 weeks.		
	Key secondary efficacy endpoint 1	SE1	Response (responder/non-responder) to study drug in the LIR subgroup during Weeks 1 to 12, where a responder is defined as having 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 out of the last 4 weeks.		
	Key secondary endpoint 2	SE2	Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours.		
	Key secondary endpoint 3	SE3	Mean number of days per week with at least 1 SBM during Weeks 1 to 12.		
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat Timepoint: 12 week treatment period				
Descriptive statistics and estimate variability	Treatment group		Placebo	NAL12,5	NAL25
	Number of subjects		232	232	232
	PE		29.3%	34.9%	39.7%

	Treatment group	Placebo LIR subgroup	NAL12,5 LIR subgroup	NAL25 LIR subgroup
	Number of subjects	121	125	124
	SE1	31.4%	42.4%	46.8%
	Treatment group	Placebo	NAL12,5	NAL25
	Number of subjects	232	232	232
	SE2 (median time to first SBM (h))	37.2	19.3	12.0
	95% CI	(30.0,46.9)	(9.4,22.3)	(7.0,21.5)
	Number of subjects	231	228	226
	SE3 (mean)	1.73	2.12	2.41
	SEM	0.12	0.12	0.13

Effect estimate per comparison	PE	Comparison groups	Placebo – NAL12,5
		RR	1.188
		95% CI	(0.911,1.548)
		P-value (CMH test stratified to laxative response status at baseline)	0.202 (NS)
	PE	Comparison groups	Placebo – NAL25
		RR	1.348
		95% CI	(1.045,1.739)
		P-value (CMH test stratified to laxative response status at baseline)	0.021
	SE1	Comparison groups	Placebo – NAL12,5 LIR subgroup
		RR	1.350
		95% CI	(0.967,1.884)
		P-value	0.074 (NS)
	SE1	Comparison groups	Placebo – NAL25 LIR subgroup
		RR	1.489
		95% CI	(1.078,2.058)
		P-value	0.014

Notes	The effect sizes for the PE endpoint and first key secondary endpoint response rate were not reported as such but as RR. The 25% effect size in response rate (treatment versus placebo) based on the response over 4 weeks from the Phase 2b study, for which the phase 2 study was designed, was not reached by any of these endpoints based on response over 12 weeks. The 25 mg naloxegol treatment effect, primary endpoint, is borderline statistically significant

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

Comparison of results in sub-populations

To explore the uniformity of the treatment effect of naloxegol across patient subgroups, additional analyses were conducted on the primary outcome variable on pooled data from Studies 04 and 05. The purpose of these analyses was to explore whether or not the treatment effect is comparable across clinically relevant OIC subgroups and to exclude the possibility that the overall treatment effect was confounded by larger than expected treatment effect in one subgroup. With the exception of the LIR subgroup, the exploratory analyses were not designed or powered to detect differences between the treatment groups, and no adjustments for multiple comparisons were made.

The following subgroups were selected for analysis: age (<50, 50-64, ≥65 years of age), gender, race (caucasian, black, and other), region (US and Europe), laxative response (LIR, non-LIR, and 2xLIR), BMI (<30 kg/mg2 and ≥30 kg/mg2), use of strong anticholinergics, maintenance opioid type ("weak" and "strong opioids"), and opioid dose (<200 meu/day and ≥200 meu/day).

A comparison versus placebo of the response to study drug in the pooled subgroups from Studies 04 and 05 for the naloxegol 12.5 mg group and the naloxegol 25 mg group are presented in Figure 1 and Figure 2, respectively.

Figure 1 Response (naloxegol 12.5 mg vs placebo) to study drug during Weeks 1 to 12 in subgroups of interest – pooled data, Studies 04 and 05 (Intent-to-treat analysis set)

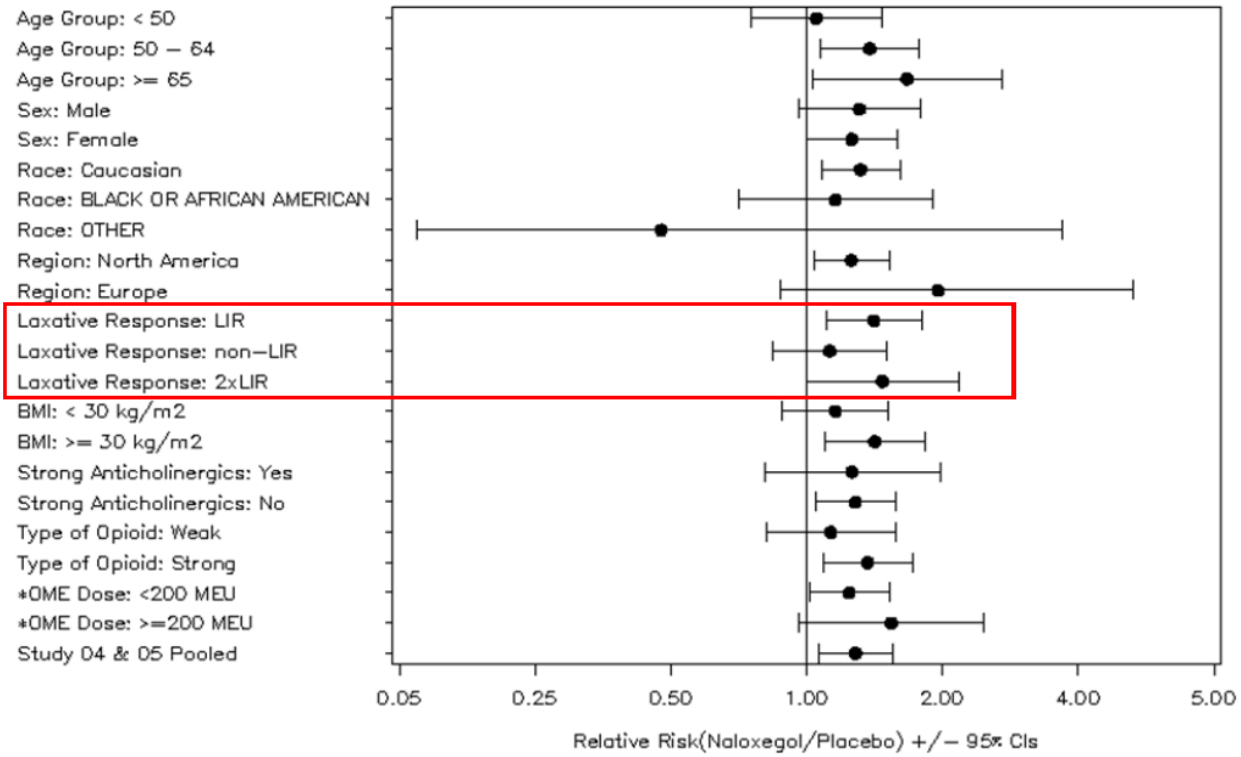
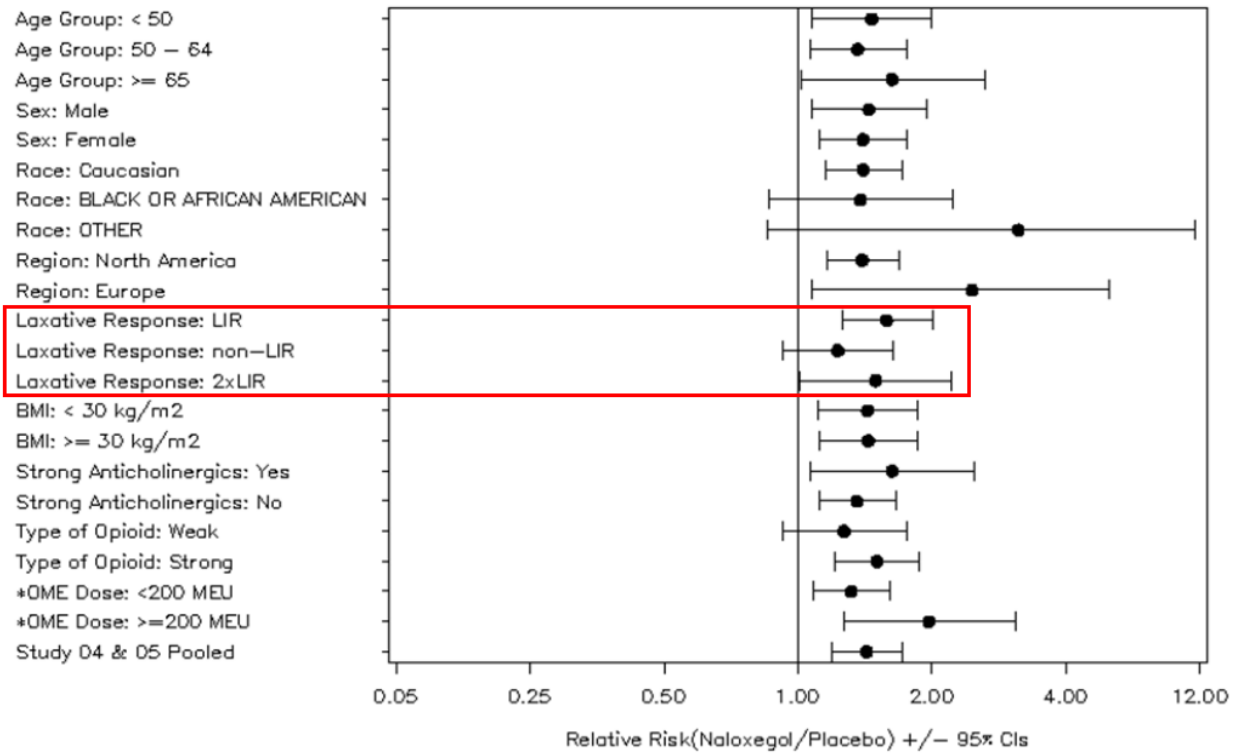


Figure 2 Response (naloxegol 25 mg vs placebo) to study drug during Weeks 1 to 12 in subgroups of interest – pooled data, Studies 04 and 05 (Intent-to-treat analysis set)



Efficacy of naloxegol in the treatment of OIC was not limited to any specific patient subgroup. The confidence intervals are wide for the RR of the "other" category within the subgroup of race for both the naloxegol 12.5 mg and 25 mg groups compared with the placebo groups, because of the small number of patients in that category (15, 11, and 6, in the placebo, naloxegol 12.5 mg, and naloxegol 25 mg groups, respectively), However, within all subgroups analyzed, confidence intervals around the treatment effect spanned those obtained for the overall population (Study 04 and 05 pooled).

Although the treatment effect was consistent across all subgroups analyzed, a detailed discussion of response by baseline maintenance opioid (dose and type), and laxative response status is presented below.

Baseline maintenance opioid (dose and type)

Response to naloxegol was assessed in subgroups of patients taking high versus low opioid doses (≥200 meu/day and < 200 meu/day, respectively) and in patients taking weak versus strong opioids. Approximately 80% of patients were receiving low doses of opioids at baseline (< 200 meu/day) and approximately 67% of patients were taking strong maintenance opioids at baseline in Studies 04 and 05.

Overall, there was a higher response rate in the naloxegol groups compared with the placebo groups in all subgroups by baseline maintenance opioid dose and type, and the treatment effect of naloxegol increased with dose.

A numerically larger treatment effect was observed in the high opioid dose group (≥200 meu/day) compared with the lower opioid dose group (<200 meu/day), which may be due to the lower placebo response rate observed in the high dose group (22.7%) compared with that of the lower opioid dose group (31.2%). In both of these subgroups, the response rate in the naloxegol 25 mg group was consistent with that seen in the overall population (44.9% and 41.1% in the high and low opioid dose

groups, respectively). Logistic regression of treatment-by baseline opioid dose in the individual studies failed to demonstrate a statistically significant treatment by baseline opioid dose interaction for either the naloxegol 12.5 mg or 25 mg groups. All of these analyses support the conclusion that naloxegol provides therapeutic benefit, regardless of opioid dose.

There also appeared to be a trend towards a numerically larger treatment effect for naloxegol in the strong opioid subgroup compared with the weak opioid subgroup. A similar trend was noted in the pharmacometric modeling analysis where opioid type (weak vs strong) was the only baseline covariate meeting the threshold for inclusion in the final model. However, analysis of response rate by specific maintenance opioid at baseline (eg, oxycodone, hydrocodone, etc) demonstrates that CIs for each of the subgroups spanned those obtained in the overall population (Study 04 and 05 pooled).

The median daily opioid dose was higher in the strong opioid group (132.5 meu/day) compared with the weak opioid group (45.0). Therefore, it is difficult to make any conclusions regarding these noted trends; it is possible that the trends are due to the opioid dose, the characteristics of the opioid molecule (weak/strong), or random variation.

Laxative response status

LIR/non-LIR subgroups

Response to study drug during Weeks 1 to 12 by laxative response status using pooled data (Studies 04 and 05) is summarized in table 8, comparing the LIR population with the non-LIR population. The majority of patients in the non-LIR population are LUR (96.6%).

Table 8 CMH analysis of response rate for Weeks 1 to 12 by laxative response status – pooled data, Studies 04 and 05 (Intent-to-treat analysis set)

	LIR			Non-LIR		
	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg
n	239	240	241	207	205	205
Number (%) of patients responding	72 (30.1)	102 (42.5)	115 (47.7)	59 (28.5)	66 (32.2)	72 (35.1)
RR (Comparison vs. placebo)[a]	NA	1.410	1.584	NA	1.126	1.230
95% CI	NA	1.106, 1.797	1.253, 2.001	NA	0.840, 1.509	0.926, 1.635
p-value	NA	0.005	<0.001	NA	0.429	0.153

[a] Analysis via Cochran Mantel-Haenszel test stratified by study.
Note: Response rate is based on the number of patients in the ITT analysis set in each treatment group.
CI confidence interval; ITT Intent-to-treat; NA Not applicable; RR Relative risk (a RR >1 is indicative of higher response rate on the naloxegol arm).

In both the LIR and non-LIR subgroups, the number and percentage of patients responding increased with dose. **However the magnitude of the treatment difference compared with placebo was larger in the LIR subgroup compared with the non-LIR subgroup.** Improvements over placebo in change from baseline in mean SBMs/week and number of days per week with at least 1 SBM were also larger in the LIR subgroup compared to the non-LIR subgroup.

In the LIR subgroups in both Studies 04 and 05, median times to first post-dose laxation was shorter in the naloxegol 12.5 mg (20.6 and 12.8 hours, respectively) and 25 mg (5.4 and 18.1 hours, respectively) groups compared with the placebo groups (43.4 and 38.2 hours, respectively). Although formal statistical testing was not performed for the non-LIR subgroup, in both Studies 04 and 05, median times to first

post-dose laxation was shorter in the naloxegol 12.5 mg (20.3 and 21.8 hours, respectively) and 25 mg (6.9 and 8.9 hours, respectively) groups compared with the placebo groups (34.8 and 33.9 hours, respectively).

Change from baseline in straining, stool consistency, and percent days per week with at least 1 CSBM over 12 weeks in both the LIR and non-LIR groups were similar for the pooled data from Studies 04 and 05 **Table 9**.

Table 9 Analyses of change from baseline in daily OIC symptom data over 12 weeks by laxative response, pooled data, Studies 04 and 05 (Intent-to-treat analysis set)

				Differences vs placebo[a]			
OIC Symptom	Subgroup	Treatment Group	n	LS Means (SEM)	LS Mean	95% CI	p-value
Straining	LIR	Placebo	238	-0.49 (0.05)	NA	NA	NA
		Naloxegol 12.5 mg	236	-0.67 (0.05)	-0.18	(-0.31, -0.05)	0.007
		Naloxegol 25 mg	238	-0.77 (0.06)	-0.28	(-0.41, -0.14)	<0.001
	non-LIR	Placebo	204	-0.53 (0.05)	NA	NA	NA
		Naloxegol 12.5 mg	203	-0.62 (0.05)	-0.09	(-0.23, 0.04)	0.182
		Naloxegol 25 mg	200	-0.74 (0.05)	-0.21	(-0.35, -0.07)	0.003
Stool Consistency	LIR	Placebo	238	0.40 (0.06)	NA	NA	NA
		Naloxegol 12.5 mg	236	0.58 (0.06)	0.18	(0.02, 0.33)	0.028
		Naloxegol 25 mg	238	0.70 (0.06)	0.3	(0.14, 0.46)	<0.001
	non-LIR	Placebo	204	0.31 (0.07)	NA	NA	NA
		Naloxegol 12.5 mg	203	0.50 (0.07)	0.19	(0.00, 0.38)	0.045
		Naloxegol 25 mg	200	0.66 (0.07)	0.35	(0.16, 0.54)	<0.001
Percent days with a CSBM	LIR	Placebo	238	16.57 (1.72)	NA	NA	NA
		Naloxegol 12.5 mg	236	25.41 (1.72)	8.83	(4.38, 13.29)	<0.001
		Naloxegol 25 mg	238	29.12 (1.78)	12.55	(8.05, 17.04)	<0.001
	non-LIR	Placebo	204	18.85 (1.66)	NA	NA	NA
		Naloxegol 12.5 mg	203	19.77 (1.70)	0.92	(-3.55, 5.40)	0.685
		Naloxegol 25 mg	200	24.07 (1.70)	5.22	(0.72, 9.72)	0.023

[a] Analysis via MMRM with fixed effects for study, baseline, baseline laxative response, treatment and treatment time interaction. Pooled centre is included as a random effect.

Note: Subject is included in the repeat statement, and an unstructured covariance matrix has been assumed.

Note: Baseline values assumed in calculating LSMEANS for the non_LIR subgroup: Straining: 3.14 Stool consistency: 2.95 Percent days with a CSBM: 6.76.

Note: Baseline values assumed in calculating LSMEANS for the non_LIR subgroup: Straining: 3.24 Stool consistency: 2.82 Percent days with a CSBM: 5.45.

LS Mean Least Squares Mean; CI Confidence Interval; NA Not Applicable.

Evaluation of demographic factors and other baseline characteristics of the LIR and non-LIR populations that potentially could explain this difference did not reveal notable differences between the two populations. Therefore, since the majority of non-LIR patients are LUR (96.6%), the only factor that appears to be different between the LIR patients and the non-LIR patients is the extent of laxative use (≥4 days or <4 days) during the 2 weeks prior to study enrolment. The reason(s) for numerically higher 12-week response rates in the LIR subgroup compared with the non-LIR subgroup in both studies are not known, at this time. Based on information from the OIC history module and laxative non-use questionnaire, it appears that many non-LIR patients had tried laxatives in the past (66% within 6 months) but had stopped them for various reasons.

2xLIR Subgroup

Using pooled data from Studies 04 and 05, the primary efficacy endpoint was also analyzed in a subgroup of patients who had inadequate response to at least 2 classes of laxatives during previous opioid treatment (2xLIRs).

Response to study drug in 2xLIR patients during Weeks 1 to 12 (Studies 04 and 05) is summarized using pooled data in **Table 10**.

Table 10 CMH analysis of response rate for 2xLIR patients – pooled data, Studies 04 and 05 (Intent-to-treat analysis set)

Treatment Group	n	Number (%) of patients responding	Comparison versus Placebo [a]		
			RR	95% CI	p-value
Placebo	90	27 (30.0)	NA	NA	NA
Naloxegol 12.5 mg	88	39 (44.3)	1.474	(0.996, 2.183)	0.050
Naloxegol 25 mg	99	44 (44.4)	1.495	(1.010, 2.213)	0.040

[a] Analysis via Cochran Mantel-Haenszel test stratified by study.
Note: Response rate is based on the number of patients in the ITT analysis set in each treatment group.
CI confidence interval; CMH Cochran Mantel-Haenszel; ITT intent-to-treat; LAR Laxative Adequate Responder/Response; LIR Laxative Inadequate Responder/Response; LUR Laxative Unknown Responder/Response; NA Not applicable; RR Relative risk (a RR >1 is indicative of higher response rate on the naloxegol arm).

The results in the 2xLIR subgroup appear consistent with those observed in the overall population.

Additional subgroup analyses

A set of post-hoc analyses were conducted to further examine the treatment effect in additional subgroups. In this analysis, the BMI was categorized as per “normal” (<25 kg/m2), “overweight,”(>25 and <30 kg/m2) and “obese” (>30 kg/m2), by categorizing the daily morphine equivalent dose into high and low categories (using a 120 meu/day threshold; this is an alternative categorization into high and low opioid doses recommended by the Washington State Medical Directors; AMDG 2010), and by the route of opioid administration (oral vs cutaneous). A caveat in the latter analysis is that many patients who were receiving opioids cutaneously (ie, transdermally) were also receiving a concomitant oral opioid. The results of these additional analyses were consistent with the subgroup analyses presented above, demonstrating a treatment effect for naloxegol compared with placebo, irrespective of the subgroup **Table11**.

Table11 Pooled unadjusted analyses of 12-week response rate. Post-hoc subgroups requested during MMA pre-submission meeting – pooled Studies 04 and 05 (Intent-to-treat analysis set)

Variable		Treatment Group	n	Number (%) of patients responding	Comparison versus Placebo[a]		
					RR	95% CI	p-value
BMI	<25 kg/m^2	Placebo	101	31 (30.7)	NA	NA	NA
		Naloxegol 12.5 mg	93	32 (34.4)	1.121	(0.748,1.678)	0.582
		Naloxegol 25 mg	78	31 (39.7)	1.282	(0.863,1.906)	0.222
	≥25 to <30 kg/m^2	Placebo	128	36 (28.1)	NA	NA	NA
		Naloxegol 12.5 mg	132	44 (33.3)	1.215	(0.845,1.748)	0.293
		Naloxegol 25 mg	139	60 (43.2)	1.525	(1.092,2.129)	0.011
	>30 kg/m^2	Placebo	217	64 (29.5)	NA	NA	NA
		Naloxegol 12.5 mg	220	92 (41.8)	1.417	(1.094,1.836)	0.007
		Naloxegol 25 mg	226	96 (42.5)	1.440	(1.115,1.860)	0.005
Total opioid dose	<120 meu	Placebo	279	85(30.5)	NA	NA	NA
		Naloxegol 12.5 mg	259	90 (34.7)	1.136	(0.889,1.451)	0.307
		Naloxegol 25 mg	273	107 (39.2)	1.286	(1.021,1.620)	0.032
	≥120 meu	Placebo	162	46 (27.9)	NA	NA	NA
		Naloxegol 12.5 mg	185	78 (42.9)	1.545	(1.148,2.081)	0.003
		Naloxegol 25 mg	173	80 (46.2)	1.653	(1.232,2.216)	0.001
Maintenance opioid route	Cutaneous	Placebo	32	10 (31.3)	NA	NA	NA
		Naloxegol 12.5 mg	44	24 (54.5)	1.743	(0.961,3.163)	0.052
		Naloxegol 25 mg	28	18 (64.3)	2.059	(1.152,3.680)	0.011
	Oral	Placebo	414	121 (29.2)	NA	NA	NA
		Naloxegol 12.5 mg	401	144 (35.9)	1.226	(1.005,1.497)	0.044
		Naloxegol 25 mg	418	169 (40.4)	1.383	(1.144,1.672)	0.001

[a] Analysis via Cochran Mantel-Haenszel test stratified by study; tests conducted within each subgroup separately.
Note: Response rate is based on the number of patients in the ITT analysis set in each treatment group.
CI confidence interval; ITT Intent-to-treat; NA Not applicable; RR Relative risk (a RR >1 is indicative of higher response rate on the naloxegol arm).

Supportive studies

- **STUDY 06 Study Code D3820C00006**

This was a Phase III, multi-centre placebo-controlled, double-blind study of NKTR-118 in patients with cancer-related pain and opioid-induced constipation (OIC).

Approximately 672 patients were planned to be enrolled to obtain 336 randomized patients. The study was originally to be conducted at approximately 150 centres in the United States and 15 other countries. Due to recruitment challenges, enrolment to this study was stopped early. At the time that enrolment was stopped, 14 patients had been enrolled at 11 centres in the US, Poland, and the Czech Republic.

Primary Objectives To compare the efficacy of NKTR-118 12.5 and 25 mg with placebo in the treatment of patients who have OIC in pain related to malignancy in a 4-week double-blind study (Part A).

Secondary Objectives To compare NKTR-118 12.5 mg and 25 mg with placebo on the daily signs and symptoms associated with OIC (degree of straining, sensation of incomplete evacuation, and stool consistency), symptoms of constipation, and overall quality of life over a 4-week double-blind study (Part A). To characterize the maintenance of effect of NKTR-118 over a 12-week extension (Part B). To assess the safety and tolerability of NKTR-118 12.5 and 25 mg, when used for the treatment of OIC.

Subject population

A total of 44 patients were enrolled in the study and of these, 14 were randomized (5 to NKTR-118 25 mg, 5 to NKTR-118 12.5 mg, and 4 to placebo). All 14 randomized patients received treatment and went on to complete Part A of the study. Of the 14 completers of Part A, 9 patients (64.3%) continued into the single-blind extension Part B of the study (3 [60.0%] in the NKTR-118 25 mg group, 3 [60.0%] in the NKTR-118 12.5 mg group, and 3 [75.0%] in the placebo group).

Results

Fourteen patients were randomized across the 3 treatment groups (fewer than 5% of the planned number), thus, there was an insufficient number of patients to perform the protocol specified formal statistical analyses.

Conclusions

Due to the small numbers of patients randomized, treatment comparisons for efficacy and safety could not be made.

- **STUDY 07 (Study code D3820C00007)**

This was a 12-week extension of the Phase III, multicenter, double-blind, randomized, placebo-controlled, parallel group 12 week study D3820C00004 to evaluate the safety and tolerability of NKTR-118 12.5 mg and 25 mg with placebo in the treatment of OIC in patients with non-cancer-related pain. Patients continued on their randomized dose from the D3820C00004 study.

NKTR-118 12.5 or 25 mg tablets, or matching placebo, administered once daily. Study drug tablets were round, biconvex, and white film coated. Tablets were supplied in high-density polyethylene bottles, dispensed every 30 days. Each 30-day supply consisted of 2 bottles of study drug, each containing 35 tablets. The duration of treatment was 12 weeks. The doses of NKTR-118 in the current study (12.5 mg and 25 mg) were the same doses as in Study D3820C00004.

Objectives

The *primary objective* of this study was to compare NKTR-118 12.5 mg and 25 mg with placebo regarding long-term safety and tolerability in the treatment of OIC using descriptive statistics.

The *secondary objectives* were to assess the impact of NKTR-118 12.5 mg and 25 mg on symptoms of constipation and quality of life using PAC-SYM and PAC-QOL questionnaires.

The *exploratory objectives* were to assess patient health status index and healthcare resource utilization.

Subject population

A total of 302 patients participated in Study D3820C00004 and continued in the double-blind treatment period of Study D3820C00007 at 52 study centers in the US (see Section 2). Similar numbers of patients were enrolled in each treatment group.

Of the patients enrolled in the current study, 297 (98.3%) received treatment, and 245 (81.1%) completed the study (defined as completing Visit 4 [Week 24] for patients who continued into the D3820C00008 long-term safety study, or completing Visit 5 [Week 26] for patients who did not continue into the long-term study).

Summary of main efficacy results

The improvement for PAC-SYM and PAC-QOL across all 3 treatment groups observed in the 12-week confirmatory study in OIC patients was maintained in this extension study.

Following the withdrawal of study treatment, there was a trend towards worsening in PAC-SYM and PAC-QOL domain scores in all treatment groups. The worsening was numerically larger in the NKTR-118 treated groups compared with placebo, particularly in the PAC-SYM satisfaction domain.

- **Study 08 D3820C00008**

This was a Phase III, 52-week, multi-center, open-label, randomized (2:1), parallel group, safety and tolerability study of NKTR-118 versus usual care in the treatment of OIC in patients with non-cancer-related pain. This was to have been a study with global participation, but all patients ended up being enrolled from the US.

Target subject population and sample size

Patients entering the study could enrol directly from 12-week pivotal study D3820C00005, directly from the 3-month safety extension (Study D3820C00007) of the 12-week pivotal study D3820C00004, or could be "new patients" who had not previously participated in a NKTR-118 study. Patients who enrolled from a previous study had no break or pause in treatment.

Sample size

No formal sample size calculation was performed for this long-term safety study. The sample size determination was based on the regulatory exposure requirement (ICH E1 [1994]) that at least 300 patients had to complete 6 months of treatment with NKTR-118 25 mg and the number of patients randomized could have been adjusted during the study in order to achieve approximately 100 patients with at least 12 months of exposure to NKTR-118.

Duration of treatment

The study duration was 54 to 58 weeks. New patients underwent an initial screening period lasting up to 2 weeks, a 2-week OIC confirmation period (during which the diagnosis of OIC and stability of opioid regimen were confirmed), and a 52-week treatment period, followed by a 2-week follow-up period.

Statistical methods

No formal statistical analyses were planned for any of the endpoints collected in this study.

Subject population

A total of 2393 patients enrolled, of which 2309 were new patients and 84 were roll-over patients. Of the 2309 new patients who entered the initial study period, 760 patients completed the OIC confirmation period, were randomized, and entered the open-label treatment period. In addition, 84 roll-over patients were also randomized. Of the 844 patients randomized, a total of 288 patients (34.1%) who received treatment discontinued the study for any reason: 36.8% in the NKTR-118 25 mg group, and 28.8% in the Usual Care group. The most common reasons for study withdrawal were patient decision (12.8%) and AE (7.2%). A greater proportion of patients withdrew due to AE in the NKTR-118 25 mg group (9.9%) compared with the Usual Care group (1.8%), primarily driven by GI AEs.

Efficacy results

For the NKTR-118 25 mg treatment group, use of rescue medication was low and stable over the treatment period.

Safety results

Long-term exposure to NKTR-118 25 mg, up to 52 weeks, was generally safe and well tolerated in the treatment of OIC patients with non-cancer related pain.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of naloxegol in the treatment of OIC in non-cancer pain was assessed in the two phase III clinical trials D3820C00004 and D3820C00005. The studies enrolled adult patients with confirmed OIC in non-cancer pain according to predefined inclusion and exclusion criteria. The doses of naloxegol used in the Phase III program (ie, 12.5 and 25 mg qd) were selected to explore the dosing regimen associated with optimal benefit/risk. The naloxegol 25 mg qd dose was selected based on efficacy and tolerability demonstrated in the 4-week Phase IIb study. In order to continue exploring the threshold for a minimally efficacious dose, the 12.5 mg qd dose was included in the Phase III program. The dose selection was supported by pharmacometric modelling.

In line with ICH Guideline E10, placebo was used to provide control for normal disease course and other non-specific factors. During the design and conduct of the Phase III program, no oral treatments for OIC had consistently demonstrated efficacy in clinical trials for this condition or had been approved by Health Authorities for use in this indication. Naloxegol in this program in non-cancer pain patients has been studied as maintenance monotherapy and not as an add-on therapy to laxatives.

The studies were performed as randomised placebo controlled trials and adequately designed with 90% power to detect a 25% difference in response between treatment and placebo. An active control arm including treatment with standard laxatives could have put the efficacy of naloxegol in perspective, especially as the endpoint of the studies aimed to show prolonged treatment efficacy but trials 04 and 05 can be considered broadly in line with the current draft guideline on the clinical investigation of medicinal products for the treatment of chronic constipation.

The primary efficacy study endpoint assessed both the magnitude and duration of treatment effect in the study population (number of responders). The first key secondary endpoint assessed the number of responders in the LIR subgroup, a subgroup of patients that responds inadequately to standard laxatives. Since about half of patients suffering from OIC do not respond adequately to standard laxatives, there appears to be a medical need for additional therapeutic options in this patient population. Notable occurrences during the conduct of the Phase III studies are summarized here. To address these, applicant declared that appropriate actions were taken: 1) Patients who had previously or concurrently participated in the naloxegol program at another study center were identified prior to database lock of each study, and were excluded from relevant analysis sets in each study. The number of such patients was small (15 in Studies 04 and 05, and 16 in Study 08) and similar between treatment groups; 2) After initial locking of the database for Study 05, data associated with one patient that was previously assessed as non-retrievable was found to be retrievable. Following applicant standard operating procedures this was considered a critical error, thus, these data were added to the database and the database was again locked and underwent a final analysis; and 3) an internal site audit, identified data integrity issues affecting 2 sites in Study 08. All patients from these sites (24 patients, 4 of these were patients who previously or concurrently participated at other study centers) were excluded from the safety analyses of the study.

The implementation of protocol amendments (please refer to description of the studies above) did not have a significant effect on the composition of the study population or the interpretation of the study results.

Efficacy data and additional analyses

Efficacy was measured as response rate in the study population, being the primary endpoint, in duplicate studies 04 and 05, investigating the effect of naloxegol 12.5 mg and 25 mg versus placebo treatment.

In study D3820C00004 relevant efficacy and durability of effect of Naloxegol was tested through the primary endpoint of response to study drug, as defined by >3 SBMs per week and a change from baseline of >1 SBM per week for at least 9 out of the 12 study weeks and 3 out of the last 4 weeks of the study. For a patient to be considered a responder under this definition of response, a durable improvement in SBMs had to have been observed over the entire 12-week treatment period. A statistically significant improvement for the primary variable was observed for both Naloxegol dose groups compared with the placebo group, with the difference in responder rate meeting a clinically relevant difference of 10% for both doses.

Similar results were observed for the response rates in the LIR subgroup, a key secondary endpoint. Statistical significance was also observed for both Naloxegol dose groups compared with placebo for the other key secondary endpoints; time to first post-dose SBM and mean number of days per week with at least 1 SBM. The median time to first post-dose SBM was 35.8, 20.4, and 5.9 hours for the placebo, 12.5 mg and 25 mg NKTR-118 groups, respectively, demonstrating a clinically relevant improvement.

All secondary endpoints, as well as sensitivity analyses of the primary endpoint, were supportive of and consistent with the primary endpoint that established a clinically relevant durable efficacy over 12 weeks. The observed treatment effect in the LIR subgroup was numerically greater than in the non-LIR subgroup across the primary and most secondary endpoints. There was no significant interaction between baseline opioid dose and response to NKTR-118 within the dose range of opioids studied. Some other secondary endpoints, which were not included in the multiple testing procedure, supported the efficacy of Naloxegol 25 mg in the treatment of OIC.

A numerical improvement in straining, stool consistency and mean % days per week with at least 1 CSBM was observed for the Naloxegol 25 mg group compared to the placebo group; the improvement in straining and stool consistency was numerically modest. The results of PAC-SYM and PAC-QOL scales are mostly negative (ie. there were not statistically significant in comparison to placebo).

The results of study D3820C00005 can be summarized as follows:

- Statistically significant higher response rates were observed in the Naloxegol 25 mg treatment group compared with placebo over 12 weeks in patients with OIC ($p=0.021$). The Naloxegol 12.5 mg dose did not demonstrate statistical significance for the primary variable ($p=0.202$), and as such, statistical significance could not be claimed for key secondary variables regardless of effect.
- In the pre-specified LIR subgroup, statistically significant higher response rates were observed in the Naloxegol 25 mg group compared with placebo over 12 weeks in patients with OIC who had inadequate response to laxatives in the past ($p=0.014$). The p-value for the Naloxegol 12.5 treatment group compared with placebo was 0.074.
- Statistically significant shorter time to first post-dose SBM was observed in the Naloxegol 25 mg treatment group compared with placebo ($p<0.001$). The unadjusted p-value for the Naloxegol 12.5 treatment group compared with placebo was <0.001.

- There was a statistically significant increase in the mean number of days per week with at least 1 SBM at Week 12 in the Naloxegol 25 mg treatment group compared with placebo ($p<0.001$). The unadjusted p-value for the Naloxegol 12.5 mg treatment group compared with placebo was 0.010.
- Improvement was observed for all individual OIC symptoms assessed (straining, stool consistency, days/week with CSBM) in the Naloxegol 25 mg (<0.001 for all) and 12.5 mg ($p=0.005$, $p=0.001$, and $p=0.002$, respectively) treatment groups compared with placebo.
- Results from analysis over 4 weeks were consistent with the results over 12 weeks.
- Improvement in the severity of symptoms of constipation in OIC patients by Week 12 was observed for the stool domain and rectal domain of PAC-SYM in the Naloxegol 25 mg treatment group compared with placebo ($p<0.001$ for both domains). There was no relevant difference in the magnitude of improvement for the abdominal domain of PAC-SYM across treatment groups by Week 12 ($p=0.279$).
- There was an improvement in quality of life for all treatment groups. For the satisfaction domain of PAC-QOL, improvement compared with placebo was observed for both the Naloxegol 25 mg and 12.5 mg treatment groups at Week 12 ($p<0.001$ and $p=0.011$, respectively).

In summary in study 05 no statistical significance for the primary endpoint of the 12.5 mg arm and borderline statistical significance for the 25 mg naloxegol arm were shown. Response rates for the 25 mg naloxegol group were 44.4% and 39.7% (placebo: 29.4% and 29.3%) in studies 04 and 05, respectively, for the primary endpoint, and 48.7% and 46.8% (placebo: 28.8% and 31.4%) in studies 04 and 05, respectively, for the first key secondary endpoint (i.e. the response rate in the LIR subgroup).

A 10% - 15% treatment effect compared to placebo was demonstrated in studies 04 and 05 for both the primary and first key secondary endpoint. This effect was higher in the LIR subgroup than in the non-LIR subgroup of patients.

The totality of the data presented in the LIR subgroup provides evidence to support a clinically meaningful benefit in these patients. The clinical relevance of the treatment effect is less clear in the general population of non-LIR patients, which is likely to be a heterogeneous group. The treatment effects in the overall study population appear to be driven by the data of the LIR subgroup in both trial 04 and 05.whereas only modest treatment effect was seen in the non LIR subgroup.

The applicant attempted a large global dedicated study in the cancer patient population suffering from OIC, but due to severe and persistent recruitment challenges, enrollment had to be stopped early. There is no published evidence that opioid receptor pharmacology, density, or location in cancer pain patients is substantially different from that of non-cancer pain patients. Therefore, there appear to be no scientific rationale to expect the pharmacodynamic properties of naloxegol to differ in this patient population. This assumption has been considered acceptable by the CHMP. Additional safety data will be collected post authorization on an ongoing basis as outlined in the RMP so that a patient population with high medical need is not deprived of the option to seek benefit with a new oral treatment option.

The totality of the data, in the LIR subgroup, provides evidence to support a clinically meaningful benefit in these patients. From the data presented by the company, the clinical relevance of the treatment effect is less clear in the general population of non-LIR patients, which is likely to be a heterogeneous group. Therefore, following analysis of the data provided, the applicant proposes to limit the therapeutic indication to adult OIC patients with an inadequate response to laxatives.

In addition, due to the limited data in this population the following wording was introduced in the SmPC section 4.3 and 4.4:

Section 4.3 Contraindications

(…)

Conditions in patients with cancer pain

- Patients with underlying cancer who are at heightened risk of GI perforation, such as those with:
  - underlying malignancies of gastrointestinal tract or peritoneum
  - recurrent or advanced ovarian cancer
  - vascular endothelial growth factor (VEGF) inhibitor treatment.

4.4 Special warnings and precautions for use

[…]
Cancer related pain
There is limited clinical experience with the use of naloxegol in OIC patients with cancer-related pain. Therefore, caution should be used when prescribing naloxegol to such patients (see section 4.3).
[…]

2.5.4. Conclusions on the clinical efficacy

The efficacy of naloxegol (12.5 and 25 mg) was assessed in two pivotal phase III clinical trials in the general non-cancer OIC population and the LIR subgroup of patients typed by an inadequate response to standard laxatives, with the primary endpoint being the percentage of responders versus placebo. The primary efficacy endpoint was assessed over a period of 12 weeks to reflect the chronic nature of the treatment. The effect sizes observed in study 05 are much smaller than in study 04 resulting in absence of statistical significance for the primary endpoint of the 12.5 mg naloxegol arm and borderline statistical significance for the 25 mg treatment arm. The observed absolute and relative treatment effects are smaller than expected: an absolute effect of 39.7 % and 44.4% with 60% expected and a relative effect over placebo of 10.4% and 15% with 25% expected in studies 05 and 04, respectively, in the 25 mg naloxegol treatment arm. The effect size appears not to be sufficient to warrant a first line therapeutic indication in the general patient population with OIC, although head to head comparison with standard laxatives and similar drugs could be very informative to evaluate the true relative effect of naloxegol, especially since the primary endpoint of this study incorporated the assessment of treatment over a prolonged period of 12 weeks.

As mentioned before, the treatment response rate is clearly imbalanced between LIR and non-LIR subgroup with the LIR response driving the general treatment response. The CHMP therefore considers that a clinically relevant treatment effect is observed in the LIR subgroup of OIC patients. The indication has been adapted accordingly to the use to LIR population only.

It is not anticipated that the method of action or the efficacy of the product will change in OIC patients with cancer-related pain. However, some of these patients may present with additional safety issues, for which a contraindication was added in the SmPC as outlined in above discussion. In addition it is outlined in the SmPC that based on the limited experience with the use of naloxegol caution should be used when prescribing the drug to such patients. Safety in these patients will be monitored closely and the missing information will additionally be addressed within a PASS as detailed in the RMP.

2.6. Clinical safety

Patient exposure

The safety of naloxegol was investigated in 4 Phase III studies and 1 Phase IIb study in patients with OIC taking opioid analgesics. In addition, 3 biopharmaceutical studies and 11 clinical pharmacology studies provide safety data. All of these studies were complete at the time of the data cut off (see Table 1).

In the Phase IIb and III naloxegol clinical studies, 1497 unique patients were exposed to naloxegol at 1 or more doses (33 to 5 mg, 446 to 12.5 mg, 999 to 25 mg, and 35 to 50 mg) and included in the safety analyses. For the 25 mg dose, 464 patients were exposed for at least 24 weeks, 317 were exposed for at least 51 weeks, and 96 were exposed for at least 52 weeks. In addition, 438 volunteers were exposed to naloxegol in the Phase I studies (at doses of 5 to 1000 mg). The recommendations for minimal patient exposure to the product in a clinical program for long term treatment of non-life threatening conditions were fully respected.

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term safety data
Placebo-controlled	1816	1176	1108	0
Open studies	804	534	534	534

Table 12**: Patient exposure in the clinical trials**

The Phase III data are the main source for evaluating safety and tolerability of naloxegol. The primary analyses sets are the 12-week pool (Study 04 and 05) and Study 08 for long-term safety data (52 weeks). Supporting data pools were also used to help characterize naloxegol's safety and tolerability profile. These include the following pools: 24-week integrated dataset (Studies 04 and 07), placebo-controlled pool (Studies 04, 05, and 07), Phase IIb/III AE pool for all OIC patients, and the Phase I pool. Other studies contributing safety data involve the Phase IIb study and the Phase III study 06.

Study code	Type of the study	NGL and comparator group	Duration
Phase III studies with non cancer related pain and OIC			
D3820C00004 (study 04)	Double blind, randomize, PBO-controlled, evaluating safety and efficacy	PB0 (N=213) NGL 12,5mg (N=211) NGL 25mg (N=214)	12 weeks
D3820C00005 (study 05)	Double blind, randomize, PBO-controlled, evaluating safety and efficacy	PB0 (N=231) NGL 12,5mg (N=230) NGL 25mg (N=232)	12 weeks
D3820C00007 (study 07)	Double blind extension of study 04, randomize, PBO-controlled, evaluating safety and efficacy	PB0 (N=100) NGL 12,5mg (N=94) NGL 25mg (N=97)	12 weeks
D3820C00007 (study 07)	Open label, long term safety and tolerability study	Usual Care (N=270) NGL 25mg (N=534)	52 weeks
Phase III studies with cancer related pain and OIC			
D3820C00006 (study 06)	Two-part study evaluating the efficacy Part A: Double randomized,	Part A: PBO (N=4) NGL 12,5mg (N=5)	Part A: 4weeks

	PBO-controlled. Part B: open label, active treatment extension(PBO patients switched to 25mg NGL)	NGL 25mg (N=5) Part B: NGL 12,5mg (N=3) NGL 25mg (N=6)	Part B: 12weeks
Phase IIb studies with non cancer related pain and OIC			
07-IN-NX003 (Phase IIb study)	Double blind, randomize, PBO-controlled, evaluating safety and efficacy	PB0 (N=96) NGL 5mg (N=33) NGL 25mg (N=30) NGL 50mg (N=35)	4 weeks

Table 1: Phase IIb/III studies providing data for the safety evaluation

The pooling proposed is considered as acceptable. The primary pool set has been divided in short term studies (study 04 and 05) and in long term exposure (study 08), this set has been used to evaluate exposure, demographics, study withdrawals, concomitant medications, AEs (including deaths, SAEs, DAEs, and AEOSIs), laboratory data, VS, ECG, body weight/BMI, NRS, mHS, opioid dose, abuse potential, C-SSRS. On the other side, the supportive data set will be used to confirm AEs and exposure. However a potential selection bias was introduced in the study 07 and 08. Only patients that have completed the study 04 or 05 were eligible to be enrolled in the study 07 or 08. In order to provide a robust assessment of the safety, patients from the study 07 and patients who were eligible were introduced in the dataset. In the study 08, which includes a majority of newly enrolled patients, a new randomisation was performed at the beginning of the study. Therefore, long term safety study 08 has been considered as the main safety pool and the data from study 07 has only been used as additional supportive information.

Demographic characteristics are equivalent between the main studies: studies 04, 05, 07 and 08 (data not shown for clinical studies 07 and 08). Most of the patients taking Naloxegol 12,5 or 25mg are white people from North America and they are aged of approximately 50 years old. More than 60% of the patients are female taking a mean opioid morphine equivalent dose (MED) of 148 meu for 45 months.

Adverse events

In the 12-week pool, the incidence of SAEs was similar across treatment groups, while the incidence of any AE and the incidence of DAEs were higher in the naloxegol 25 mg group than in the placebo and naloxegol 12.5 mg treatment groups (see Table 2). In Study 08, the incidence of AEs and SAEs was similar between the Usual Care and naloxegol 25 mg groups. The incidence of DAEs could not be compared between treatments, because patients in the Usual Care group were not taking IP and therefore by definition could not have a DAE. Therefore, Among patients enrolled in Study 04 or Study 05, the relative risk (vs. placebo) of experiencing at least 1 AE of any kind during the treatment period was 1.03 (95% CI: 0.85, 1.23) for patients receiving naloxegol 12.5 mg and 1.30 (95% CI: 1.09, 1.55) for patients receiving naloxegol 25 mg

AE category	12-week pool (Studies 04 and 05)			52-week safety study (Study 08)	
	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Usual care[a] (N=270)	NGL 25 mg (N=534)
Any AE	227 (51.1)	231 (52.4)	283 (63.5)	194 (71.9)	428 (80.1)
Any AE with outcome = death	0	0	0	1 (0.4)	0
Any SAE (including events with outcome = death)	20 (4.5)	20 (4.5)	14 (3.1)	30 (11.1)	46 (8.6)
Any DAE	21 (4.7)	20 (4.5)	46 (10.3)	NA	50 (9.4)

[a] Patients randomized to Usual Care were treated with approved over-the-counter and/or prescription laxative(s) either as monotherapy or in any combination, according to the Investigator's clinical judgment. These patients were not taking IP and therefore could not discontinue IP.

Table 2: Number of patients who had 1 or more AE in any category during the treatment period

The most frequently reported AEs were primarily **GI AEs**, which is not unexpected given the naloxegol mechanism of action, moreover most adverse events were mild to moderate in intensity. They tended to occur during the first 7 days of treatment for all doses, although in the naloxegol 25 mg group, they were reported later as well (see Table 3).

Preferred term	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)
Patients with any AE	227 (51.1)	231 (52.4)	283 (63.5)
Abdominal pain	25 (5.6)	43 (9.8)	71 (15.9)
Diarrhea	19 (4.3)	25 (5.7)	41 (9.2)
Nausea	20 (4.5)	29 (6.6)	36 (8.1)
Flatulence	11 (2.5)	13 (2.9)	26 (5.8)
Headache	12 (2.7)	17 (3.9)	20 (4.5)
Vomiting	13 (2.9)	10 (2.3)	20 (4.5)
Back pain	9 (2.0)	12 (2.7)	19 (4.3)
Abdominal pain upper	7 (1.6)	8 (1.8)	17 (3.8)
Hyperhidrosis	1 (0.2)	2 (0.5)	13 (2.9)
Abdominal distension	9 (2.0)	11 (2.5)	11 (2.5)
Upper respiratory tract infection	12 (2.7)	9 (2.0)	11 (2.5)
Fatigue	6 (1.4)	7 (1.6)	10 (2.2)
Sinusitis	6 (1.4)	6 (1.4)	10 (2.2)
Pain in extremity	3 (0.7)	5 (1.1)	10 (2.2)
Nasopharyngitis	1 (0.2)	5 (1.1)	9 (2.0)
Fall	8 (1.8)	9 (2.0)	4 (0.9)
Dizziness	9 (2.0)	11 (2.5)	3 (0.7)

Note: Patients with events in ≥1 PT are counted once in each of those PTs. AEs that started on or after the first dose of investigational product through end of study are included. AEs are sorted by PT in decreasing order of frequency (by total number on NGL 25 mg, 12.5 mg, then placebo).

Table 3: Number of patients with the most common AEs during the 12-weeks treatment period

As in the 12-week pool, in Study 08, the most common AEs among naloxegol-treated patients were **abdominal pain, diarrhoea, and nausea** (respectively 17.8% vs. 3.3% in the Usual Care group,

12.9% vs. 5.9% in the Usual Care group, and 9.4% vs. 4.1% in the Usual Care group). In addition, the following AEs had an incidence ≥5% in the naloxegol 25 mg group and at least twice the incidence in the Usual Care group: flatulence (6.9% vs. 1.1%) and abdominal pain upper (5.1% vs. 1.1%). In the long term, the first onset of AEs of abdominal pain, headache, and flatulence was more frequently reported during the initial 12-week period.

Analysis of adverse events of special interest

- As peripherally acting mμ-opioid receptor antagonist, NGL such as methylnaltrexone, may be involved in GI perforation event. All patients at increased risk of GI perforation were excluded from clinical trials and no AEs reported as bowel perforation in any naloxegol-treated patient were detected. The potential risk of developing GI perforation upon NGL is adequately addressed in the product information.
- In an alvimopan long-term safety study in 805 patients with opioid bowel dysfunction, increased rates of CV events such as myocardial infarction (MI) were observed. According to the prescribing information for alvimopan, "A causal relationship with alvimopan has not been established."; therefore, the implications of this isolated finding for alvimopan and for the PAMORA class are unclear. However, to ensure that the risk of MACE was fully understood, all serious CV events (and selected non-serious CV AEs of interest) occurring in the Phase III clinical studies of naloxegol were adjudicated by an independent external CV event adjudication committee (CV-EAC). The incidence of CV-related AEs in the Phase III program with onset during either the treatment period or the post-treatment follow-up period that were severe, serious, and/or led to discontinuation of naloxegol was low and similar across treatment groups in the 12-week pool (1.4% for placebo and naloxegol 12.5 mg, 1.6% for naloxegol 25 mg) and in Study 08 (2.9% for Usual Care and 2.1% for naloxegol 25 mg). Overall, no clinically important CV safety signal was observed in the naloxegol clinical program. Decrease and increased BP events were also similar between treatment groups. On the other syncope incidents were only detected in the NGL groups and should be further investigated by the Applicant (see Table 4).

	Placebo-controlled pool (Studies 04/07 and 05)			52-week safety study (Study 08)	
Topic/ Preferred term	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Usual care (N=270)	NGL 25 mg (N=534)
Decreased BP	**3 (0.7)**	**2 (0.5)**	**6 (1.3)**	**5 (1.9)**	**5 (0.9)**
Hypotension	1 (0.2)	2 (0.5)	3 (0.7)	1 (0.4)	1 (0.2)
BP decreased	2 (0.5)	0	2 (0.4)	3 (1.1)	3 (0.6)
Orthostatic hypotension	0	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)
Syncope	**0**	**2 (0.5)**	**2 (0.4)**	**0**	**3 (0.6)**
Syncope	0	2 (0.5)	1 (0.2)	0	3 (0.6)
Presyncope	0	0	1 (0.2)	0	0
Increased BP	**5 (1.1)**	**10 (2.3)**	**13 (2.9)**	**12 (4.4)**	**21 (3.9)**
Hypertension	3 (0.7)	6 (1.4)	8 (1.8)	9 (3.3)	13 (2.4)
BP increased	2 (0.5)	4 (0.9)	3 (0.7)	3 (1.1)	7 (1.3)
Accelerated hypertension	0	0	1 (0.2)	0	0
Malignant hypertension	0	0	1 (0.2)	0	0
BP diastolic increased	0	0	0	0	1 (0.2)

Table 4: Number of patients with one or more AE related to blood pressure change during the treatment period.

- Naloxegol has limited capacity to pass through the blood-brain barrier, and thus central opioid antagonism is unlikely at doses relevant to its anticipated use in patients with OIC. However, to better understand and quantify any theoretical risk of CNS opioid antagonism, pain intensity (as measured by the NRS and opioid dose) were continually assessed throughout the Phase III studies. Following study 04 and 05, based on both mean daily average pain scores and mean worst pain scores from daily diary entries, there was no evidence that naloxegol interfered with analgesia: there were no clinically important changes in NRS pain scores from baseline in any treatment group. For the naloxegol 25 mg group in the 12-week pool (Studies 04 and 05), there was a small imbalance in the frequency of (sometimes overlapping) reports of back pain and pain in extremity, while no treatment imbalances were detected in the longer-term studies, Studies 07 and 08. After a careful review, this small imbalance in the 12-week pool does not appear to be causally related or clinically important. Moreover there were no unexpected, clinically meaningful trends (increasing or decreasing) in daily opioid dose with the use of naloxegol. More patients in the NGL groups presented with mHS signs (see Table 5), hyperhidrosis is the most frequent symptom, in most of the patients this symptom is associated with GI AEs

	12-week pool (Studies 04 and 05)			52-week safety study (Study 08)	
	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Usual care (N=270)	NGL 25 mg (N=534)
Any sign[a]	**4 (0.9)**	**8 (1.8)**	**22 (4.9)**	**4 (1.5)**	**25 (4.7)**
Hyperhidrosis	2 (0.5)	2 (0.5)	13 (2.9)	1 (0.4)	17 (3.2)
Tremor	3 (0.7)	4 (0.9)	5 (1.1)	1 (0.4)	3 (0.6)
Rhinorrhoea	0	1 (0.2)	3 (0.7)	1 (0.4)	4 (0.7)
Yawning	1 (0.2)	0	2 (0.4)	0	3 (0.6)
Lacrimation increased	0	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)
Piloerection	0	0	1 (0.2)	0	0
Restlessness	1 (0.2)	0	0	0	5 (0.9)
Mydriasis	0	0	0	0	0

[a] The sign Hyperhidrosis was matched to the preferred terms hyperhidrosis, night sweats, and cold sweats. The sign tremor was matched to the preferred terms tremor and feeling jittery. The sign restlessness was matched to the preferred terms restlessness and akathisia. All other signs were matched directly to MedDRA preferred terms.

Table 5: Number of patients with AEs related to the mHS signs during the treatment period

Serious adverse event / deaths / other significant events

There were a total of 7 deaths in naloxegol clinical program: 5 in the Phase III studies, 1 in the Phase II study, and I in the Phase I studies. Of the 6 deaths in OIC patients, 1 occurred in the Usual Care group in Study 08 (0.4%), 3 occurred in patients in naloxegol 12.5 mg groups (0.7%), and 2 occurred in patients in naloxegol 25 mg groups (0.2%, 1 in Phase III, 1 in Phase IIb). No common etiological basis was identified; furthermore, neither the Investigator nor the applicant consider any of these individual cases to be related to study treatment.

The incidence of SAEs was similar across treatment groups, with no dose ordering and no SOC or PT predominating. Pneumonia was the most frequently reported SAE overall, with no notable imbalance in frequency across treatment groups (incidence <1% in all groups).

Laboratory findings

Review of pooled and individual study haematology data, clinical chemistry data and urinalysis parameter did not reveal any notable imbalance between treatment groups for any parameter with respect to mean changes, shifts from normal baseline values to abnormal on-treatment values, or the pattern or frequency of PCI values. However a small imbalance can be detected for the TSH level. A review of the individual cases revealed that the small imbalance in low TSH level incidence is mostly due to pre-existing

hypothyroidism in 16 patients treated with levothyroxine (14 in the NGL 25 mg group). These patients were not subject to an increased incidence of GI AEs (see Table 6).

	12-week pool (Studies 04 and 05)			52-week safety study (Study 08)[a]	
Parameter and ERR2 limit	Placebo n/N (%)	NGL 12.5 mg n/N (%)	NGL 25 mg n/N (%)	Usual care n/N (%)	NGL 25 mg n/N (%)
Sodium ≤120 mmol/L	0/432	0/431	0/418	1/228 (0.4)	0/470
Sodium ≥160 mmol/L	0/432	1/431 (0.2)	1/418 (0.2)	0/228	0/470
Potassium ≤2.6 mmol/L	0/430	2/431 (0.5)	0/418	0/226	0/470
Potassium ≥6.4 mmol/L	2/430 (0.5)	5/431 (1.2)	0/418	0/226	4/470 (0.9)
Creatinine ≥265 µmol/L	1/432 (0.2)	0/431	0/418	0/228	0/470
Fasting glucose ≥13.9 mmol/L	8/218 (3.7)	5/226 (2.2)	2/208 (1.0)	7/127 (5.5)	9/260 (3.5)
Non-fasting glucose ≥22.2 mmol/L	2/244 (0.8)	1/244 (0.4)	2/253 (0.8)	0/152	2/326 (0.6)
AST ≥5 x ULN	2/432 (0.5)	1/431 (0.2)	1/418 (0.2)	0/228	0/470
ALT ≥5 x ULN	2/432 (0.5)	1/431 (0.2)	1/417 (0.2)	2/228 (0.9)	2/470 (0.4)
Total cholesterol ≥10.36 mmol/L	1/405 (0.2)	0/403	1/385 (0.3)	0/12	0/34
Leukocyte count ≤1.5 x 10^9/L	0/431	0/431	0/419	1/228 (0.4)	0/470
Erythrocyte count ≤3.0 x 10^{12}/L, Male	1/153 (0.7)	0/153	0/169	0/77	0/156
Neutrophils, ABS ≤1.00 x 10^9/L	1/431 (0.2)	2/431 (0.5)	0/419	2/228 (0.9)	3/470 (0.6)
TSH ≤0.1 uIU/mL	12/431 (2.8)	7/431 (1.6)	12/418 (2.9)	2/228 (0.9)	16/469 (3.4)
TSH ≥20 uIU/mL	0/431	3/431 (0.7)	1/418 (0.2)	1/228 (0.4)	7/469 (1.5)

[a] For Study 08, only patients who had not previously participated in a naloxegol trial, approximately 90% of the study population, are included. Results for rollover patients are presented in Module 5.3.5.2, Study 08 clinical study report,

Table 6: Summary of PCI laboratory abnormalities during the treatment period

Safety in special populations

A population PK analysis was conducted. Among the demographic and baseline characteristics included in the covariate analysis (i.e., age, race, sex, weight, baseline creatinine clearance, type of opioid, opioid dose, baseline laxative responder status, concomitant weak/moderate/strong CYP3A4 inhibitor/inducer, concomitant P-gp inhibitor/inducer), only race and concomitant administration of strong and moderate CYP3A4 inhibitors showed significant changes in naloxegol exposure. Among Black subjects, slightly (20%) lower exposure was observed. Among Asian subjects, a reduced volume of distribution resulting in a 25-30% higher Cmax was observed. These findings regarding the effects of race were considered to be small differences with limited impact.

No apparent differential effect of naloxegol was detected on either overall AE incidence or the incidence of AEs by SOC and PT based on sex, age, race, BMI, geographic region, baseline LIR/non-LIR status, or baseline opioid dose, where the number of subjects was large enough to allow interpretation of the results. For patients with a baseline opioid dose of at least 200 meus, there was a higher incidence of AEs across all treatment groups, particularly in the GI SOC. Nearly 75% of the patients treated with an opioid dose ≥200 meu had an AEs and 70% of these AEs were in the gastro-intestinal SOC. In the long term safety study, an increase of AEs prevalence was also detected for patients taking high dose of opioid (see Table 7).

The results of Study 09 indicate that subjects with moderate to severe renal impairment have higher average Cmax and AUC than subjects with normal renal function. Despite the higher average exposure in moderately and severely renal-impaired subjects, the safety profile of naloxegol in subjects with renal

impairment at baseline was similar to patients with normal baseline creatinine clearance values. Furthermore, the subjects with unusually high exposure in the moderate and severe renal impairment groups exhibited no differences in tolerability profile. There were no clinically relevant changes in laboratory, vital sign, ECG or physical exam data in the subjects enrolled in Study 09.

	Placebo		NGL 12.5 mg		NGL 25 mg	
	N	n (%)	N	n (%)	N	n (%)
Subjects with ≥1 AE	**444**	**227 (51.1)**	**441**	**231 (52.4)**	**446**	**283 (63.5)**
Sex						
Male	159	81 (50.9)	160	78 (48.8)	181	110 (60.8)
Female	285	146 (51.2)	281	153 (54.4)	265	173 (65.3)
Age						
<65 years	394	196 (49.7)	397	209 (52.6)	393	253 (64.4)
≥65 years	50	31 (62.0)	44	22 (50.0)	53	30 (56.6)
Race						
White	342	182 (53.2)	347	193 (55.6)	362	240 (66.3)
Black	87	40 (46.0)	83	36 (43.4)	78	40 (51.3)
Other	15	5 (33.3)	11	2 (18.2)	6	3 (50.0)
BMI						
<30 kg/m^2	228	115 (50.4)	222	114 (51.4)	217	127 (58.5)
≥30 kg/m^2	216	112 (51.9)	219	117 (53.4)	226	153 (67.7)
Geographic region						
North America	416	210 (50.5)	418	222 (53.1)	423	272 (64.3)
Europe	27	16 (59.3)	23	9 (39.1)	23	11 (47.8)
Baseline laxative response						
LIR	238	119 (50.0)	237	120 (50.6)	241	152 (63.1)
Non-LIR	206	108 (52.4)	204	111 (54.4)	205	131 (63.9)
Baseline opioid dose						
<200 meu	356	174 (48.9)	345	167 (48.4)	348	210 (60.3)
≥200 meu	88	53 (60.2)	96	64 (66.7)	98	73 (74.5)

AE Adverse event; LIR Laxative inadequate responder; meu Morphine equivalent unit; N Total number of subjects in treatment group and subgroup; n Number of subjects meeting criteria; NGL Naloxegol.

Table 7: Number of subjects with AEs during the treatment period, by subgroup.

The observed AE profile was similar between patients <65 years of age compared with patients >65 years of age. The lower number of patients >65 years of age makes comparative assessments of low-frequency events challenging. For most of the event categories in the table below, the AE rate was similar between those <65 years of age and ≥65 years of age. SAE rates for placebo and Usual Care cohorts were 7.5% and 14.7%, respectively, for patients ≥65 years of age and 6.1% and 10.7%, respectively, for patients <65 years of age.

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)
Total AEs	268 (68.2%)	28 (65.1%)	3 (30.0%)	0
Serious AEs – Total	16 (4.1%)	5 (11.6%)	0	0
- Fatal	0	0	0	0
- Hospitalization/prolong existing hospitalization	15 (3.8%)	5 (11.6%)	0	0
- Life-threatening	2 (0.5%)	0	0	0
- Disability/incapacity	0	0	0	0
- Other (medically significant)	5 (1.3%)	2 (4.7%)	0	0
AE leading to drop-out	44 (11.2%)	6 (14.0%)	0	0
Psychiatric disorders	17 (4.3%)	3 (7.0%)	0	0
Nervous system disorders	38 (9.7%)	3 (7.0%)	0	0
Accidents and injuries	20 (5.1%)	3 (7.0%)	1 (10.0%)	0
Cardiac disorders	10 (2.5%)	3 (7.0%)	0	0
Vascular disorders	19 (4.8%)	4 (9.3%)	0	0
Cerebrovascular disorders	2 (0.5%)	0	0	0
Infections and infestations	86 (21.9%)	8 (18.6%)	1 (10.0%)	0
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	15 (3.8%)	3 (7.0%)	0	0
<other AE appearing more frequently in older patients>	0	0	0	0

PTs included = Orthostatic hypotension, Fall, Syncope, Presyncope, Vertigo, Dizziness postural, Dizziness, Ataxia, Gait disturbance, Fracture, Upper limb fracture, Ankle fracture, Tooth fracture, Foot fracture, Wrist fracture, Rib fracture, Fibula fracture, Upper limb fracture, Thoracic vertebral fracture, Tibia fracture, Clavicle fracture, Hand fracture, Scapula fracture, Stress fracture, Radius fracture, Ulna fracture, Loss of consciousness.

Cerebrovascular Disorders (SMQ) = ischaemic cerebrovascular conditions (SMQ), haemorrhagic cerebrovascular conditions (SMQ), conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ), and cerebrovascular disorders, not specified as haemorrhagic or ischaemic (SMQ).

MedDRA Medical Dictionary for Regulatory Activities; PT preferred term; SMQ Standardised MedDRA query; SAE serious adverse event; SOC system organ class

Safety related to drug-drug interactions and other interactions
Drug/food interaction

The effect of eating a meal prior to administration of naloxegol was studied in biopharmaceutical studies. The clinical studies have shown that exposure (i.e., AUC) increases by 42% to 55% and maximum plasma concentration increase by 30% to 47% when a 25 mg dose of naloxegol is administered after eating a meal, compared with fasting conditions. A related statement was added in the SmPC mentioning that naloxegol should be taken on an empty stomach at least 30 minutes prior to the first meal of the day.

Drug/drug interaction

In vitro data indicate that naloxegol is a substrate of CYP3A as well as a P-gp transporter, and that CYP3A is the major CYP enzyme responsible for the metabolism of naloxegol. Thus the metabolism, distribution (e.g. CNS penetration) and disposition of naloxegol may be altered by drugs that interfere with CYP3A or P-gp. As such, studies of interactions between naloxegol and morphine, ketoconazole, rifampin, quinidine, and dilitazem have been conducted as part of the naloxegol clinical development program. There was no important difference in the frequency or pattern of AEs between patients who received

moderate or strong CYP3A4 inhibitors during the study and the overall safety population. Specified amendments have been added in the SmPC.

A post hoc analysis of AEs in the subgroup of patients taking methadone was conducted when it was observed that these patients were disproportionately represented in the small group of patients with AEs of opioid withdrawal. All of the patients on methadone with AEs of opioid withdrawal had concurrent GI AEs. GI AE rates during the study were higher in the subgroup of patients in the 12-week pool who were taking methadone than in the overall safety population, particularly in the naloxegol 25 mg group. In the 12 weeks study, more than 80% of the patient treated with methadone and NGL 25mg had AEs, mostly a GI AEs (see Table 8). For this specific population, approximately 25% of the patients will experience AEs under the NGL 25mg treatment that they would not have under the placebo treatment. The potential for a pharmacodynamic interaction at the opioid receptor has been characterised. Since both methadone and naloxegol bind to opioid receptors in the GI tract, an interaction was expected. Many of the side effects of naloxegol in the GI tract may reflect supra-pharmacological effects; that is, improved GI peristalsis may lead to GI cramps, and reduced water absorption may lead to diarrhoea. Unlike morphine, methadone is efficient at inducing μ-opioid receptor endocytosis, an important mechanism in ensuring that desensitised and internalized receptors are rapidly recycled to the cell surface in an active form, maintaining receptor signalling, and reducing receptor desensitisation and tolerance development. This reason appropriately explains the AEs occurring with concomitant use of Naloxegol and methadone. In the long term safety study, patients who were receiving methadone as long term treatment were excluded from the study.

	Placebo	NGL 12.5 mg	NGL 25 mg
Safety analysis set			
N	444	441	446
n (%) with any AE	236 (53.2%)	241 (54.6%)	291 (65.2%)
n (%) with any GI AE	96 (21.6%)	117 (26.5%)	166 (37.2%)
Subroup of patients on methadone			
N	29	18	32
n (%) with any AE	16 (55.2%)	10 (55.6%)	26 (81.3%)
n (%) with any GI AE	7 (24.1%)	7 (38.9%)	24 (75.0%)

AE Adverse event; GI Gastrointestinal; N Total number of patients; NGL Naloxegol.

Table 8: Incidence of any AE and any AE during the treatment or post treatment period: overall population and patients on methadone.

Discontinuation due to adverse events

In the 12-week pool, most DAEs occurred during the first 4 weeks of treatment. The most common DAEs among naloxegol-treated patients in the 12-week pool were diarrhoea, abdominal pain, and nausea (see Table 9). The overall DAE rate was higher in the naloxegol 25 mg group than in both of the other groups, which appeared to be driven predominantly by treatment differences in the incidence of diarrhoea and abdominal pain DAEs.

	12-week pool (Studies 04 and 05)			12-week extension of Study 04 (Study 07)			52-week safety study (Study 08)	
	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Placebo (N=100)	NGL 12.5 mg (N=94)	NGL 25 mg (N=97)	Usual care[a] (N=270)	NGL 25 mg (N=534)
Any DAE	**24 (5.4)**	**21 (4.8)**	**46 (10.3)**	**3 (3.0)**	**4 (4.3)**	**4 (4.1)**	**NA**	**56 (10.5)**
Diarrhea	3 (0.7)	4 (0.9)	14 (3.1)	0	1 (1.1)	0	NA	11 (2.1)
Abdominal pain	1 (0.2)	4 (0.9)	13 (2.9)	0	0	0	NA	9 (1.7)
Nausea	1 (0.2)	5 (1.1)	5 (1.1)	1 (1.0)	0	0	NA	3 (0.6)
Abdominal pain upper	0	0	5 (1.1)	0	0	0	NA	2 (0.4)
Vomiting	1 (0.2)	2 (0.5)	4 (0.9)	1 (1.0)	0	0	NA	5 (0.9)
Hyperhidrosis	1 (0.2)	0	4 (0.9)	0	0	0	NA	3 (0.6)
Back pain	1 (0.2)	1 (0.2)	2 (0.4)	0	0	0	NA	1 (0.2)
Myalgia	0	0	2 (0.4)	0	0	0	NA	1 (0.2)
Liver function test abnormal	0	0	2 (0.4)	0	0	0	NA	0
Headache	0	0	2 (0.4)	0	0	0	NA	1 (0.2)
Flatulence	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0	NA	2 (0.4)
Depression	0	1 (0.2)	1 (0.2)	0	0	0	NA	2 (0.4)
Hypotension	0	1 (0.2)	1 (0.2)	0	0	1 (1.0)	NA	0
Fatigue	1 (0.2)	0	1 (0.2)	1 (1.0)	0	0	NA	3 (0.6)
Chills	0	0	1 (0.2)	0	0	0	NA	3 (0.6)
Influenza like illness	0	0	1 (0.2)	0	0	0	NA	2 (0.4)
Dizziness	1 (0.2	2 (0.5)	0	0	0	1 (1.0)	NA	0
Abdominal discomfort	0	1 (0.2)	0	0	0	0	NA	2 (0.4)
Abdominal pain lower	0	0	0	0	0	0	NA	2 (0.4)
Arthralgia	0	0	0	0	0	0	NA	2 (0.4)

a Patients in the Usual Care group in Study 08 were not taking investigational product and therefore could not have DAEs.
Note: DAEs are sorted by preferred term by highest incidence on naloxegol 25 mg, then naloxegol 12.5 mg, then placebo in the 12-week pool; followed by naloxegol 25 mg in Study 08; then by naloxegol 25 mg, then naloxegol 12.5 mg, then placebo in Study 07.

Table 9: Number of patients who had a DAE that was reported for 2 patients or more in any treatment group.

The frequency and pattern of DAEs in Study 08 were similar to those seen in the naloxegol 25 mg group in the 12-week studies. Note that patients in the Usual Care group were not taking IP and therefore could not have DAEs.

2.6.1. Discussion on clinical safety

The safety of NGL was investigated in 4 phase III studies and 1 Phase IIb study. Four studies were double-blind, randomized, placebo-controlled (study 04, 05, 07 and phase IIb) while one long term study was open label vs usual care (study 08). The duration of the placebo controlled studies was 12 weeks (except 4 weeks for the Phase IIb study) which is appropriate regarding the indication. 12,5 and 25mg daily doses of NGL were evaluated in short- and mid-term study while only 25mg daily doses were tested on long term study (52 weeks).

The pooling strategy of the patients involved in these studies is considered acceptable. The primary pool set has been divided in short term (study 04 and 05) and long term exposure (study 08), this population has been used to evaluate exposure, demographics, study withdrawals, concomitant medications, AEs (including deaths, SAEs, DAEs), laboratory data, VS, ECG, body weight/BMI, NRS, mHS, opioid dose, abuse potential. The supportive data set is composed of four patient populations, one of those is the 24 weeks integrated data set (study 07), the placebo controlled pool (study 04, 05 and 07), the phase IIb/phase III pool and the Phase I pool.

- The incidence of SAEs was similar across treatment groups with no dose ordering and no SOC or PT predominating. Pneumonia was the most frequently reported SAE, with no notable imbalance in frequency across treatment groups. Patient's narratives for these SAEs were reviewed and did not point any safety concern.
- Seven deaths occurred during the clinical programs but none of these individual cases was considered to be related to the study treatment.
- The incidence of common AEs (especially gastrointestinal AEs) was higher for patients upon NGL 25mg treatment. The most frequently reported AEs were GI AEs (abdominal pain, diarrhoea, nausea, flatulence, ...). They tended to occur in the first 7 days and their numbers are dose dependant. The Applicant considers that these GI AEs are not unexpected considering the pharmacological properties of NGL.
- During 12 weeks study, the overall DAE rate was higher in the naloxegol 25 mg group and appeared to be driven predominantly by the incidence of severe diarrhoea and abdominal pain. No conclusion can be drawn regarding the proportion of patients who have completed the 52 weeks study considering that patients in the usual care group may at any time modify the treatment and/or the posology.
- No clinically important CV safety signals were observed during the studies. However, a small imbalance in the incidence of increase BP and syncope events was detected and further investigated by the Applicant. These events were added to the RMP as Important and Potential risks respectively and a PASS to characterize the CV risk and Major Adverse Cardiac Events such as MI, CVA, and cardiac death has been included in the Pharmacovigilance plan of the RMP.
- According to pain measurement (NRS pain scores), NGL did not interfere with analgesia and no unexpected changes in daily opioid doses were detected. Despite some imbalance in reporting of hyperhidrosis and pain, no clear signs of opioid withdrawal symptoms were detected during NGL treatments. Nevertheless the risk of opioid withdrawal cannot be totally excluded and is mentioned in the SmPC.
- In vitro data and PK analyses indicate that naloxegol is a substrate of CYP3A as well as a P-gp transporter but there was no important difference in the frequency or pattern of AEs between patients who received moderate or strong CYP3A4 inhibitors during the study and the overall safety population.
- Patients with a baseline opioid dose of at least 200 meus or taking methadone, presented higher incidence of AEs across all treatment groups, particularly in the GI SOC. The Applicant proposed as explanation that the number and the activity of the opioid receptor have decreased with the "down regulation of opioid receptors". The remaining receptors become more active and sensitive, leading to higher effects of the NGL therapy and also to higher reporting of GI AEs. In this context, the Applicant proposed a reduced starting dose of 12,5mg for patients treated with opioid at higher dose than 200meus or treated with methadone. Nevertheless, Naloxegol 25 mg has also a higher incidence of AE compared to 12.5 mg indicating only a limited impact on the number of treatment responders and suggesting that most clinically important GI AEs or DAEs occur in non-responders. Therefore, the most efficacious dose, 25 mg naloxegol, should be used in these patients. If patients do not tolerate the 25 mg naloxegol dose, treatment can be lowered to a 12.5 mg dose.

2.6.2. Conclusions on the clinical safety

Naloxegol at doses up to 25 mg once daily was generally safe and well tolerated in patients with OIC. Nonetheless a notable imbalance identified between treatment and placebo groups in clinical trials was GI AEs. The incidence and the duration of the GI AEs was dose dependent and began at the early stage of the treatment. This difference may lead to a serious increase of DAEs in the 25mg NGL groups and may be related to the daily opioid dose taken by the patients. At high doses of opioids, the number and the activity of the opioid receptors are falling and the patient becomes more sensitive to the effect of NGL leading to increased activity and increased number of GI AEs. If the initial dose is not tolerated by the patient of this subgroup, a reduction to 12.5mg daily may be implemented. On the other hand, the risk of MACE, reversal of analgesia and other opioid withdrawal symptoms was correctly assessed according to robust safety data. Patients at increased risk of GI perforation were excluded from clinical studies and therefore the impact of NGL on these patients could not be studied. All these potential risks are addressed in the SmPC and PIL documents.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 5.0 with the following content:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 10: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Clinically important GI AEs Opioid withdrawal syndrome Interactions with drugs modulating CYP3A4 and P-gp activities
Important potential risks	GI perforation Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope) Off-label use

	Interference with opioid-mediated analgesia
Missing information	Efficacy/safety in methadone-treated population Efficacy/safety in cancer pain population Efficacy/safety in High risk CV patients Efficacy/safety beyond 1 year Efficacy/safety in patients >75 years of age Efficacy/safety in patients with severe renal impairment (creatinine clearance <30 mL/min) Efficacy/safety in patients with hepatic impairment Efficacy/safety in non-Caucasian and non-African-Americans/Black patients Efficacy/safety in Paediatric populations Efficacy/safety in Pregnancy/lactation

The PRAC agreed.

Pharmacovigilance plan

Table 11: Ongoing and planned studies in the PhV development plan

Study/Activity Type, t**itle** and **category 1-3)**	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
Study D3820C00016 (Category 3, relevant to existing areas of uncertainty)	Multiple dose PK and safety in paediatric ages ≥6 months to <18 years	Missing information regarding safety in paediatric patients	3Q2014	CSR by 2Q2017
Proposed and pending approval: Naloxegol Post-Market Observational Drug Utilisation Study (D2288R00081) Category 3, relevant to existing areas of uncertainty)	To describe demographic, clinical, and treatment characteristics in the baseline of patients treated with naloxegol To describe treatment pattern characteristics of naloxegol utilisation at initiation and follow-up	Potential identified and potential risks. Missing information.	AZ will submit a protocol to the EMA no later than January 2015. AZ will target agreement of the protocol with the EMA during 1Q2015	2018
Proposed and pending approval: Naloxegol Post-Market Observational Safety Study in Patients Taking Opioids for	To estimate event rates for pre-specified health outcomes of interest among naloxegol-treated patients with active cancer pain	Potential identified and potential risks. Missing information.	AZ will submit a protocol to the EMA no later than January 2015.	First annual report delivered by the end of 4Q2016 and every year thereafter until completion

Study/Activity Type, t**itle** and **category 1-3)**	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
Cancer Pain (D2288R00082) Category 3, relevant to existing areas of uncertainty)			AZ will target agreement of the protocol with the EMA during 1Q2015	
Proposed and pending approval Naloxegol Post-Market Observational Safety Study in Patients Taking Opioids for non-Cancer Pain (D2288R00084, Category 3, relevant to existing areas of uncertainty	To estimate event rates for pre-specified health outcomes of interest among naloxegol-treated patients with non-cancer pain.	Potential identified and potential risks. Missing information.	AZ will submit a protocol to the EMA no later than January 2015. AZ will target agreement of the protocol with the EMA during 1Q2015	First annual report delivered by the end of 4Q2016 and every year thereafter until completion
Proposed and pending approval A US post-marketing, comparative, observational study to evaluate the cardiovascular safety of naloxegol in patients with non-cancer pain in comparison to other treatments for opioid induced constipation	This observational study will characterize the CV risk and Major Adverse Cardiac Events such as MI, CVA, and cardiac death.	CV risk	Final Protocol Submission to the FDA for approval and to the EMA for information: May 2015. Study Completion: December 2021	Final report: December 2023 Annual reports: Starting in 2016 until study completion. Reports* will be in the form of a progress report unless replaced by an interim report in a given year per an agreed upon schedule with FDA

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

Risk minimisation measures

Table 12: Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks		

Clinically important GI AEs	Section 4.4 (Special warnings and precautions for use) of the SmPC contains the following: *Reports of severe abdominal pain and diarrhoea have been observed in clinical trials with the 25 mg dose, typically occurring shortly after initiation of treatment. There was a higher incidence of discontinuations in patients taking the 25mg dose compared to placebo due to diarrhoea (0.7% for placebo versus 3.1% for naloxegol 25 mg) and abdominal pain (0.2% versus 2.9%, respectively). Patients should be advised to promptly report severe, persistent or worsening symptoms to their physician. Consideration may be given to lowering the dose to 12.5mg in patients experiencing severe gastrointestinal adverse events depending upon the response and tolerability of individual patients.* Statement within Section 4.8 (Undesirable effects) of the SmPC lists the following terms: *Abdominal pain* *Diarrhoea* *Flatulence* *Nausea* *Vomiting*	None
Opioid Withdrawal Syndrome	Section 4.4 (Special warnings and precautions for use) of the SmPC contains the following statement: *Clinically important disruptions of the blood-brain barrier:* *Naloxegol is a peripherally acting mu-opioid receptor antagonist with restricted access to the central nervous system (CNS). The blood-brain barrier integrity is important for minimizing naloxegol uptake into the CNS. Patients with clinically important disruptions to the blood-brain barrier (e.g. primary brain malignancies, CNS metastases or other inflammatory conditions, active multiple sclerosis, advanced Alzheimer's disease etc.) were not included in clinical studies and may be at risk for naloxegol entry into the CNS. Naloxegol should be prescribed with caution in such patients taking into account their individual benefit-risk balance with observation for potential CNS effects, such as symptoms of opioid withdrawal and/or interference with opioid mediated analgesia. If evidence for interference with opioid mediated analgesia or opioid withdrawal syndrome occurs, patients should be instructed to discontinue Moventig and contact their physician.* Section 4.8 (Undesirable effects) of the SmPC lists opioid withdrawal syndrome with a	None

	frequency of uncommon and the following note: *Naloxegol at therapeutic doses has minimal uptake across the blood-brain barrier. In some patients, however, a constellation of symptoms has been reported, which resembles the syndrome of central opioid withdrawal. Most such reports were observed shortly after initial administration with the drug and were mild or moderate in intensity.*	
Interactions with drugs modulating CYP3A4 or P-gp activities	SmPC Section 4.4 (Special warnings and precautions for use): *Moventig is not recommended in patients who are taking strong CYP3A4 inducers (see section 4.4).* SmPC Section 4.5: *<u>Interaction with CYP3A4 inhibitors and inducers</u>* *<u>Interaction with strong CYP3A4 inhibitors</u>* *In an open-label, non-randomized, fixed-sequence, 3-period, 3-treatment, crossover study to evaluate the effect of multiple doses of ketoconazole on the single dose PK of naloxegol, co-administration of ketoconazole and naloxegol resulted in a 12.9-fold (90% CI: 11.3-14.6) increase naloxegol AUC and a 9.6-fold increase in naloxegol Cmax (90% CI: 8.1-11.3), compared to when naloxegol was administered alone. Therefore, concomitant use with strong CYP3A4 inhibitors is contraindicated (see section 4.3). Grapefruit juice has been classified as a potent CYP3A4 inhibitor when consumed in large quantities. No data are available on the concomitant use of naloxegol with grapefruit juice. Concomitant consumption of grapefruit juice while taking naloxegol should generally be avoided and considered only in consultation with a healthcare provider (see section 4.4).* *<u>Interaction with moderate CYP3A4 inhibitors</u>* *In an open-label, nonrandomized, fixed-sequence, 3-period, 3-treatment, crossover study to evaluate the effect of multiple doses of diltiazem on the single dose PK of naloxegol, co-administration of diltiazem and naloxegol resulted in a 3.4-fold (90% CI: 3.2-3.7) increase in naloxegol AUC and a 2.9-fold increase in naloxegol Cmax (90% CI: 2.6-3.1), compared to when naloxegol was administered alone. Therefore, a dose-adjustment of naloxegol is recommended when co-administered with diltiazem and other moderate CYP3A4 inhibitors (see section 4.2). The starting dose for patients taking moderate CYP3A4 inhibitors is 12.5 mg once daily and the dose can be increased to 25 mg if 12.5 mg is well*	None

	tolerated by the patient (see section 4.2). *No dosage adjustment is required for patients taking weak CYP3A4 inhibitors.* *Interaction with strong CYP3A4 inducers* *In an open-label, nonrandomized, fixed-sequence, 3-period, 3-treatment, single-dose, crossover study to evaluate the effect of multiple doses of rifampin on the single dose PK of naloxegol, co-administration of rifampin and naloxegol resulted in a 89% (90% CI: 88%-90%) decrease in naloxegol AUC and a 76% decrease in naloxegol Cmax (90% CI: 69%-80%), compared to when naloxegol was administered alone. Therefore, Moventig is not recommended in patients who are taking strong CYP3A4 inducers (see section 4.4).* *Interaction with P-gp inhibitors* *A double-blind, randomized, 2-part, crossover, single center study was conducted to evaluate the effect of quinidine on the pharmacokinetics of naloxegol and the effect of the co-administration of naloxegol and quinidine on morphine-induced miosis in healthy volunteers. Co-administration of the P-gp inhibitor quinidine resulted in a 1.4 fold increase in the AUC (90% CI: 1.3-1.5) and a 2.4 fold increase in the Cmax (90% CI: 2.2-2.8) of naloxegol. Co-administration of naloxegol and quinidine did not antagonize the morphine-induced miosis effect, suggesting that P-gp inhibition does not meaningfully change the capacity of naloxegol to cross the blood-brain barrier at therapeutic doses.* *As the effects of P-gp inhibitors on the PK of naloxegol were small relative to the effects CYP3A4 inhibitors, the dosing recommendations for Moventig when co-administered with medicinal products causing both P-gp and CYP3A4 inhibition should be based on CYP3A4 inhibitor status - strong, moderate or weak - (see sections 4.2, 4.3 and 4.5).* Other dual P-gp and strong CYP3A4 inhibitors include clarithromycin, telaprevir, ritonavir, and conivaptan.	
Important potential risks		
GI perforation	Section 4.3 (Contraindications) of the SmPC contains the following statement: *Patients with known or suspected gastrointestinal obstruction or in patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation (see section 4.4).* Section 4.4 (Special warnings and precautions for use) of the SmPC contains the following	None

	statement: *Rare cases of gastrointestinal perforation have been reported in the post-marketed use of peripherally acting mu-opioid receptor antagonists in patients with advanced medical illness. Caution with regards to the use of naloxegol should be exercised in patients with any condition which might result in impaired integrity of the gastrointestinal tract wall (e.g. severe peptic ulcer disease, Crohn's Disease, active or recurrent diverticulitis, infiltrative gastrointestinal tract malignancies or peritoneal metastases). The overall benefit-risk profile for each patient should be taken into account. Patients are advised to discontinue therapy with naloxegol and promptly notify their physician if they develop unusually severe or persistent abdominal pain.*	
Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope)	SmPC Section 4.4(Special warnings and precautions for use) of the SmPC contains the following statement: *Patients with CV conditions* *Naloxegol was not studied in the clinical trial programme in patients who had a recent history of myocardial infarction within 6 months, symptomatic congestive heart failure, overt cardiovascular (CV) disease or patients with a QT interval of ≥ 500msec. Moventig should be used with caution in these patients. A QTc study performed with naloxegol in healthy volunteers did not indicate any prolongation of the QT interval.*	None
Off-label use		None
Interference with opioid-mediated analgesia	Statement within SmPC Section 4.4 (Special warnings and precautions for use): *Naloxegol is a peripherally acting mu-opioid receptor antagonist with restricted access to the central nervous system (CNS). The blood brain barrier integrity is important for minimizing naloxegol uptake into the CNS. Patients with clinically important disruptions to the blood-brain barrier (e.g. primary brain malignancies, CNS metastases or other inflammatory conditions, active multiple sclerosis, advanced Alzheimer's disease etc.) were not included in clinical studies and may be at risk for naloxegol entry into the CNS. Naloxegol should be prescribed with caution in such patients taking into account their individual benefit-risk balance with observation for potential CNS effects, such as*	None

	symptoms of opioid withdrawal and/or interference with opioid-mediated analgesia. If evidence for opioid-mediated interference with analgesia or opioid withdrawal syndrome occurs, patients should be instructed to discontinue Moventig and contact their physician	
Missing information		
Efficacy / safety in methadone-treated population	Statement within SmPC section 4.4 (Special warnings and special precautions for use): *Concurrent methadone use* *Patients taking methadone as primary therapy for their pain condition were observed in clinical trials to have a higher frequency of gastrointestinal adverse events (such as abdominal pain and diarrhoea) than patients not receiving methadone. In a few cases, symptoms suggestive of opioid withdrawal when taking naloxegol 25 mg were observed in patients taking methadone for their pain condition. This was observed in a higher proportion of patients taking methadone than those not taking methadone. Patients taking methadone for treatment of opioid addiction were not included in the clinical development program and use of naloxegol in these patients should be approached with caution.*	None

Efficacy / safety in cancer population	Statement within SmPC Section 4.3 (Contraindications):
	Conditions in patients with cancer pain
	• *Patients with underlying cancer who are at heightened risk of GI perforation, such as those with:*
	  • *Underlying malignancies of gastrointestinal tract or peritoneum*
	  • *Recurrent or advanced ovarian cancer*
	Vascular endothelial growth factor (VEGF) inhibitor treatment.
		None

Efficacy / safety in high CV risk paitents	Statement within SmPC section 4.4 (Special warnings and special precautions for use): Patients with CV conditions *Naloxegol was not studied in the clinical trial programme in patients who had a recent history of myocardial infarction within 6 months, symptomatic congestive heart failure, overt cardiovascular (CV) disease or*	None

	patients with a QT interval of≥ 500msec. Moventig should be used with caution in these patients. A QTc study performed with naloxegol in healthy volunteers did not indicate any prolongation of the QT interval.	
Efficacy / safety beyond 1 year of exposure	Efficacy/safety not studied beyond 52 weeks. Statement within SmPC Section 5.1 (Pharmacodynamic properties): *Long-term exposure to naloxegol 25 mg, up to 52 weeks, was generally safe and well tolerated in the treatment of OIC patients with non-cancer-related pain. During the 52-week treatment period there were no important unexpected differences in the safety and tolerability findings between the naloxegol 25 mg treatment group and the usual care treatment group.*	None
Efficacy / safety in patients >75 years of age	SmPC Section 4.2: *No dose adjustment is recommended based on age (see section 5.2).* SmPC Section 5.2: *There is a small effect of age on the pharmacokinetics of naloxegol (approximately 0.7% increase in AUC for every year increase in age). No dose adjustment is recommended for elderly patients. Patients over 65 years of age have been represented in the phase III studies. Clinical studies of naloxegol did not include sufficient numbers of patients aged 75 years or over to determine whether they respond differently than younger patients, however, based on the mode of action of the active substance there are no theoretical reasons for any requirement for dose adjustments in this age group. For dose recommendations for patients with moderate or severe renal insufficiency, see section 4.2.There is no gender effect on the PK of naloxegol.*	None
Efficacy / safety in patients with severe renal impairment (<30 mL / min)	SmPC Section 4.2: *The starting dose for patients with moderate or severe renal insufficiency is 12.5 mg. If side effects impacting tolerability occur, naloxegol should be discontinued. The dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient (see section 5.2).* SmPC Section 5.2: *As renal clearance is a minor route of elimination for naloxegol, regardless of severity (i.e. moderate, severe and end stage*	None

	renal failure), the impact of renal impairment on the pharmacokinetics of naloxegol was minimal in most subjects. However, in 2 out of 8 patients (in both the moderate and severe renal impairment groups but not in the end stage renal failure group) up to 10-fold increases in the exposure of naloxegol were observed. In these patients renal impairment may adversely affect other clearance pathways (hepatic/gut drug metabolism, etc.) resulting in higher exposure. Exposure of naloxegol in end-stage renal disease (ESRD) patients on hemodialysis was similar to healthy volunteers with normal renal function.	
Efficacy / safety in patients with hepatic impairment	SmPC Section 4.2: *No dose adjustment is required for patients with mild to moderate hepatic impairment. Safety and efficacy have not been established in patients with severe hepatic impairment (see section 5.2). Use in patients with severe hepatic impairment is not recommended.* SmPC Section 4.4: *Naloxegol has not been studied in patients with severe hepatic impairment. The use of naloxegol is not recommended in such patients.* SmPC Section 5.2: *Less than 20% decrease in AUC and 10% decrease in C_{max} were observed in patients with mild and moderate hepatic impairment (Child-Pugh Class A and B). Effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of nalogexol was not evaluated. Use in patients with severe hepatic impairment is not recommended.*	None
Efficacy / safety in non-Caucasian and non–African - American Black patients	Statement within SmPC Section 5.2 (Pharmacokinetic properties). <u>Race</u> The effect of race on the pharmacokinetics of naloxegol is small (approximately 20% decrease in the AUC of naloxegol when other groups are compared to Caucasian) and, therefore, no dose adjustment is necessary	None
Efficacy / safety in Paediatric populations	Statements within SmPC Sections 4.2 (Posology and method of administration): Safety and efficacy of naloxegol have not been established in paediatric patients and 5.2 (Pharmacokinetic properties): The pharmacokinetics of naloxegol in the paediatric population have not been studied.	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

The CHMP endorses the final conclusions of the PRAC

2.9. Product information

2.9.1. User consultation

The appropriate guideline states that “Care should be taken that user testing is performed on the basis of the package leaflet as it is actually supplied with the product.” In this case, the user testing was performed on a leaflet reflecting the therapeutic indication originally applied for while only the use as a second line therapeutic indication, i.e. in OIC patients that respond inadequately to standard laxatives, can be approved. However, it is considered that the change in therapeutic indication will not substantially influence the outcome of user testing, which evaluates many more sections than the therapeutic indication only. In addition, a change in therapeutic indication does not necessitate a novel user consultation according to the corresponding guideline. The current user testing therefore can be considered sufficient.

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.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The major beneficial effect relates to the relief of opioid-induced constipation (OIC) assessed over a period of 12 weeks in non-cancer pain treated patients (primary study variable) in the subgroup of patients not responding adequately to standard laxatives (first key secondary endpoint, laxative inadequate responders (LIR) subgroup). In conjunction with this, improvement of constipation related symptoms and of quality of life data add clinical relevance to the treatment response detected.

Using 25 mg naloxegol daily, a 42% and 48% efficacy response rate was demonstrated in the overall study population and in the LIR subgroup, respectively, compared to 30% in the placebo group and 35% in the non-LIR group after 12 weeks of treatment. Statistical significance was demonstrated for the treatment response rate in the overall study population and in the LIR subgroup compared to placebo. In addition, 95% CIs surrounding the point estimates of treatment effect size indicated a reliable, positive effect of treatment compared to placebo. Although these 95% CIs were fairly wide, it is important to notice that they did not straddle the "no effect" values, with the point estimate of effect being the best and most likely estimate of the true treatment effect in the population. Similar positive results, even if borderline to significance, have been reported also for the 12.5 mg dose which can be considered as the

starting dose for patients with moderate to severe renal insufficiency or patients taking moderate CYP3A4 inhibitors. The dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient.

Uncertainty in the knowledge about the beneficial effects.

The overall response of the primary endpoint in the overall study population was mainly driven by the response in the LIR subgroup indicating a consequently clinically irrelevant response size in the non-LIR subgroup. For this reason the initially proposed first line indication was narrowed to patients who have had an inadequate response to laxative(s) to reflect the population that can clinically benefit from the use of Naloxegol.

Patient reported outcomes such as constipation symptom assessment reports (e.g. time to first laxation) and the PAC-SYM and PAC-QoL questionnaires' data were presented. Positive results in part of the domains scores analysed indicate positive effects in the use of Naloxegol. However, the clinical relevance of the PAC-QoL data is to be interpreted with caution as this questionnaire has not yet been validated in OIC patients.

It is not anticipated that the method of action or the efficacy of the product will change in OIC patients with cancer-related pain. However, some of these patients may present with specific safety issues such as heightened risk of GI perforation, for which the product is contraindicated. Safety will be monitored closely in this patient population by means of a PASS study.

Risks

Unfavourable effects

Increase in AEs

During the 12-week efficacy studies, the incidences of AEs were 51.1%, 52.4% and 63.5% respectively in the placebo, NGL 12.5 mg and NGL 25 mg. This increased incidence of AEs was confirmed in these patient groups in the 24-week integrated dataset where the overall AE rates were 51.6%, 54.6%, and 64.7% and in the 52-week study with AEs incidences of 71.9% for the usual care group and 80.1% for the NGL 25 mg group. However, the product still presents with an appropriate tolerability profile since most of the AEs were mild to moderate in intensity. On the other hand, this increase in the prevalence of AEs, although being expected given naloxegol's mechanism of action, is clearly higher compared to the usual care treatment which further supports the second line indication.

Increase in GI AEs

In all clinical trials, GI AEs are common and dose ordered. In the 25mg NGL group, the most common AEs are abdominal pain (15.9%), diarrhoea (9.2%), nausea (8.1%), flatulence (5.8%), vomiting (4.5%) and abdominal upper pain (3.8%). They tended to occur in the first weeks of treatment; however the prevalence of abdominal pain, flatulence and abdominal upper pain remains higher than placebo during the entire study. Moreover 3, 5 and 21 patients who received placebo, NGL 12.5 mg and NGL 25 mg respectively reported severe abdominal pain during the treatment period and a large part of these patients left the study. During the 52-week study, gastrointestinal AEs (abdominal pain, diarrhoea, nausea, flatulence, and abdominal upper pain) were still more common in the NGL 25 mg group compared with the usual care group. Most of these GI AEs remain also mild or moderate in intensity with a frequent onset in the first 7 days of treatment. As outlined in the SmPC consideration may be given to lowering the dose to 12.5mg in patients experiencing severe gastrointestinal adverse events depending upon the response and tolerability of individual patients.

Increase in DAEs

Likewise, the overall DAE rate was clearly higher in the NGL 25 mg group (10.3%) compared to placebo (5.4%) or NGL 12.5 mg (4.8%). Most of the DAEs occurred during the first 4 weeks of treatment and were driven by GI AEs. These discontinuations are mostly due to diarrhoea (3.1%), abdominal pain (2.9%) and nausea (1.1%). During the long term study, the frequency and the pattern of DAEs were similar. Moreover, in the 25 mg NGL group, 40.6% of the patients left the safety study (10.5% for DAEs) while only 30.7% left the placebo group. The relevant side effects are adequately taken into account in the SmPC where it is also outlined that patients should be advised to promptly report severe, persistent or worsening symptoms to their physician.

Safety issues for patients treated concomitantly with methadone and high daily dose of opioids

In the 12 weeks studies, over 80% of the patients treated with methadone and NGL 25mg had AEs, mostly GI AEs. In this specific population, approximately 25% of the patients will experience AEs under the NGL 25mg treatment that they would not have experienced under placebo treatment. An increase of AEs was also observed in the patients treated with opioid daily dose higher than 200 meus. The methadone-treated patients were excluded from the long term safety study. No interaction between methadone and NGL were detected during PK studies and this risk is considered balanced with appropriate precautionary statements within the SmPC.

Uncertainty in the knowledge about the unfavourable effects

Naloxegol is a peripherally acting selective antagonist of opioid binding at the mu-opioid receptor. Considering the fact that rare cases of gastrointestinal perforation have been reported in adult patients with the use of marketed peripherally acting mu-opioid receptor antagonists in patients with opioid-induced constipation, patients who were at risk of this AE were excluded from the clinical studies. Therefore, the risk of perforation for these patients treated with naloxegol was addressed with a contraindication in the SmPC.

Patients taking methadone as primary therapy for their pain condition were observed in clinical trials to have a higher frequency of gastrointestinal adverse events (such as abdominal pain and diarrhoea) than patients not receiving methadone. In a few cases, symptoms suggestive of opioid withdrawal when taking naloxegol 25 mg were observed in patients taking methadone for their pain condition. This was observed in a higher proportion of patients taking methadone than those not taking methadone. As patients taking methadone for treatment of opioid addiction were not included in the clinical development program the SmPC includes a precautionary statement that use of naloxegol in these patients should be approached with caution.

Patients with moderate or strong renal impairment and with hepatic impairment were also excluded from several phase IIb/III studies. Based on the pharmacokinetic profile of the product the starting dose for patients with moderate to severe renal insufficiency or patients taking moderate CYP3A4 inhibitors should be 12.5 mg. The dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient.

Despite the fact that the reporting of CV AEs is reassuring, the safety profile of NGL in these patients needs to be completed because patients at high CV risks were not included in Phase III clinical studies (patients who had a QTcF >500 msec at screening, had a recent history of myocardial infarction within 6 months before randomization, had symptomatic congestive heart failure, or had any other overt CV disease) ; for this purpose a PASS will be carried out as outlined in the risk management plan.

Benefit-risk balance

Importance of favourable and unfavourable effects

The primary study endpoint response rate is, on its own, insufficiently favourable in support of a marketing authorisation under the general indication as was originally submitted. The primary endpoint in the general population reached statistical significance, but the rather limited increase in response rate compared with placebo and the observed imbalance in response rate in two mutually exclusive subgroups, i.e. LIR and non-LIR patients, precluded the approval of the initial therapeutic indication based hereon. Unfavourable effects observed in the 25 mg naloxegol treatment arms of the phase III clinical trials were consistently higher compared to placebo.
Consequently, the lack of balanced clinically relevant beneficial treatment effects results in a negative B/R balance in the general OIC patient population.

Nevertheless efficacy results in the subgroup of patients, for which previous treatment with standard laxatives led to inadequate response, can be considered substantial and clinical relevant. They outweigh the risk of observed adverse events observed in this subgroup of OIC patients.

	Effect	Short Description	Unit	Pcbo	Nal 12,5 mg	Nal 25 mg	Uncertainties Strength of evidence Limitations
Favourable	RR LIR (pooled)	Responders in LIR subgroup	%	30.1	42.5	47.7	RR LIR = First key secondary endpoint Effect size of treatment with clinical relevance Stringent endpoint reflecting chronic condition 12.5 mg dose is to be used in case of moderate to severe renal insufficiency or when taking moderate CYP3A4 inhibitors or when patients experience severe gastrointestinal adverse events depending upon the response and tolerability of individual patients
	RR (pooled)	Responders	%	29.4	37.8	41.9	Primary Endpoint Study 05 borderline statistically significant Clinical relevance of effect size unclear since the response is imbalanced over subgroups Stringent endpoint reflecting chronic condition
	Relative risk (95% CI)	Relative response risk	ratio	---	1.280 (1.063-1.543)	1.425 (1.190-1.707)	
	RR 2xLIR (pooled)	Responders in 2xLIR subgroup	%	30	44.3	44.4	Effect size has clinical relevance Stringent endpoint reflecting chronic condition
	RR non-LIR (pooled)	Responders in non-LIR subgroup	%	28.5	32.2	35.1	Effect size not clinically relevant Stringent endpoint reflecting chronic condition
	First laxation (Study 04/05)	See below	hr	35.8/ 37.2	20.4/ 19.3	5.9/ 12.0	Immediate effect less relevant for chronic condition
	Days ≥1 SBM/w	See below	d	1.71	2.18	2.45	

	(pooled)						
	PAC-SYM (study 04/05)	Change from baseline @ w12	mean score	-0.69/ -0.63	-0.76/ -0.75	-0.81/ -0.81	Questionnaire yet to be validated in OIC.
	PAC-QoL (study 04/05)	Change from baseline @ w12	mean score	-0.89/ -0.81	-0.91/ -1.12	-1.06/ -1.30	Questionnaire yet to be validated in OIC.
Unfavourable	Gastrointestinal adverse event	See below	%	20.9	25.4	36.5	Frequency and pattern of GI AEs were confirmed during the long term safety study (52 weeks).
	Discontinuation adverse event	See below	%	5.4	4.8	10.3	10.5% of DAEs in the 52-weeks study. Most occurred in the first weeks of the treatment.
	Increase in AEs in methadone treated patients	See below	%	55.2	55.6	81.3	Serious increase in the level of AEs resulting in a NNH of 4 while NNH was 8 in treated non-methadone users. Patients treated with methadone were excluded from long term study.

Pcbo, placebo; Nal, Naloxegol; RR, response rate: a responder to study drug during Weeks 1 to 12 was defined as a patient with at least 3 SBMs/week and at least a 1 SBM/week increase over baseline for at least 9 out of the 12 treatment weeks and 3 out of the last 4 treatment weeks during the double-blind treatment period demonstrated by the primary analysis in the ITT analysis set; pooled, combined results of studies 04 and 05; LIR, laxative inadequate responder; CI, confidence interval; First laxation, median time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours; Days ≥1 SBM/w, mean number of days per week with at least 1 SBM (spontaneous bowel movement) during Weeks 1 to 12; 2xLIR, patients who had inadequate response to at least 2 classes of laxatives during previous opioid treatment; Gastrointestinal adverse event, PAC-SYM; Patient Assessment of Constipation Symptoms; PAC-QoL; Patient Assessment of Constipation - Quality of Life; Dose dependent increase of the GI AEs during 12-weeks treatment (abdominal pain, diarrhoea, nausea, flatulence, …) with duration and the intensity of the AEs also increased; Discontinuation adverse event, dose-dependent increase of the DAEs mostly driven by the increase of GI AEs; Increase in AEs in methadone treated patients, increase of AEs, DAES and opioid withdrawal symptoms was observed. GI AEs are the most popular SOC involved in DAEs; NNH, number needed to harm

Benefit-risk balance

Discussion on the benefit-risk balance

The efficacy and safety of naloxegol was mainly established in two replicate phase III double blind, placebo controlled studies in patients with OIC and non-cancer related pain. Other studies submitted were in support of the phase III efficacy and safety data.

The efficacy of the product, in the two doses proposed by the applicant and in the general OIC patient population, was of borderline clinical significance when considered in the first line indication. Further to a more in-depth analysis of subgroups evidence of clinical relevance has been clearly obtained in the LIR population; indeed, assessment of subgroup data analysis indicates that Moventig up to 25mg daily demonstrates a larger and clinically relevant effect compared to placebo in LIR patients. This is also sustained by fairly positive results in the secondary endpoints analysed. This includes positive results in

the assessment of OIC symptoms even considering the validation limitation of the Patient Report Outcome questionnaire used. Therefore, general efficacy of the product has been demonstrated in the LIR subgroup with a dose up to 25mg. Due to the pharmacokinetic profile of the product the starting dose for patients with moderate to severe renal insufficiency or patients taking moderate CYP3A4 inhibitors should be 12.5 mg. The dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient.

The safety profile of the product has demonstrated a general acceptability of the drug in the target population of LIR patients. Most common AEs, as expected, are in the GI SOC, and therefore are mainly correlated with the mechanism of action of the drug and are dose related. As outlined in the SmPC, consideration may be given to lowering the dose from 25mg to 12.5mg in patients experiencing severe gastrointestinal adverse events depending upon the response and tolerability of individual patients. According to pain measurement, Naloxegol has also demonstrated no interference on opiod analgesic effect, confirming the absence of central antagonism of the μ-receptor and reassuring that opioid withdrawal symptoms are unlikely. Nevertheless the risk of opioid withdrawal cannot be totally excluded and is mentioned in the SmPC.
Missing information on CV safety has been addressed in the RMP in which BP and syncope events have been listed as Important and Potential risks respectively and a PASS to characterize the CV risk and Major Adverse Cardiac Events such as MI, CVA, and cardiac death has been included in the Pharmacovigilance plan of the RMP. Missing information on cancer population should not reduce the possibility to consider the treatment in this subgroup of OIC patients. Indeed, it is not anticipated that the method of action or the efficacy of the product will change in OIC patients with cancer-related pain. However, some of these patients may present with high risk of GI perforation. Naloxegol is therefore contraindicated in these particular conditions. In addition safety will be monitored closely in this patient population and a PASS will be conducted as outlined in the risk management plan.

In conclusion, considering the efficacy and safety profile of the product, the B/R of naloxegol 12.5 mg and 25 mg daily for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s) is considered to be 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 Moventig in the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s) is favourable and 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.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of

Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

New Active Substance Status

Based on the CHMP review of data on the quality, the non-clinical and clinical properties of the active substance, the CHMP considers that naloxegol oxalate is qualified as a new active substance