



The European Medicines Agency  
*Evaluation of Medicines for Human Use*

EMA/CHMP/10906/2008

**ASSESSMENT REPORT  
FOR  
RELISTOR**

International Nonproprietary Name:  
**METHYLNALTREXONE BROMIDE**

**Procedure No. EMA/H/C/870**

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

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# **1 BACKGROUND INFORMATION ON THE PROCEDURE**

## **1.1 Submission of the dossier**

The applicant Wyeth Europa Limited submitted on 04 May 2007 an application for Marketing Authorisation to the European Agency for the Evaluation of Medicinal Products (EMA) for RELISTOR, through the centralised procedure falling within Article 3 (2) (a) of Regulation (EC) No 726/2004.

The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 February 2007.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended – complete and independent application.

The application submitted is a complete dossier 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 tests or studies.

The applicant applied for the following indication: Treatment of opioid-induced constipation in advanced illness patients who are receiving palliative care when response to usual laxative therapy has not been sufficient.

### **Scientific Advice:**

The applicant received Scientific Advice from the CHMP on 16 November 2006. The Scientific Advice pertained to quality and clinical aspects of the dossier.

### **Licensing status:**

The product was not licensed in any country at the time of submission of the application.

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

Rapporteur: Dr. Harald Enzmann

Co-Rapporteur: Dr Ian Hudson

## **1.2 Steps taken for the assessment of the product**

- The application was received by the EMA on 04 May 2007.
- The procedure started on 23 May 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 August 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 09 August 2007.
- During the meeting on 17-20 September 2007, 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 20 September 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 06 December 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 January 2008.
- During the CHMP meeting on 18-21 February 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP a List of Outstanding Issues on 13 March 2008.
- The Rapporteurs circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 07 April 2008.

- During the meeting on 21-24 April 2008, 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 RELISTOR on 24 April 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 23 April 2008.

## 2 SCIENTIFIC DISCUSSION

### 2.1 Introduction

Opioid analgesics are commonly administered for moderate to severe pain in a multiplicity of disorders. They are, however, consistently associated with a spectrum of debilitating side effects, including constipation, abdominal pain, discomfort, bloating, nausea and vomiting, urinary retention, and pruritus. Chronic constipation is observed in 40-70% of these patients.

Opioids cause constipation by maintaining or increasing intestinal smooth muscle tone, by suppressing forward peristalsis, by raising sphincter tone at the ileocaecal valve and anal sphincter, and by reducing sensitivity to rectal distension. Moreover, secretion and blood flow are also negatively influenced.

In patients in palliative care, with life threatening disease, the constipation caused by opioids may be altered and exacerbated by factors related to the underlying malignant or other concomitant disease, such as metabolic alterations (diabetes, hypercalcemia, hypokaliemia, uremia, hypothyroidism), dehydration, advanced age, reduced physical activity or immobility, low fluid and/or low dietary fiber intake, mechanical obstruction, neurological disorders, and concomitant medication such as antiemetics, diuretics, anticonvulsants, vinca alkaloids, and others. Moreover, and contrary to other side effects of opioids, patients very rarely develop tolerance to the constipating effects of opioids.

Complications associated with uncontrolled constipation include faecal impaction and spurious diarrhoea, pseudo-obstruction of the bowel with the symptoms abdominal pain, nausea, and vomiting and interference with drug administration and absorption.

Efficacy of conventional laxatives in opioid induced constipation has not been fully established and only small prospective studies are available with some of the substances used in the setting. Commonly, recommendations for the treatment of opioid-related constipation have been made on the basis of personal experience and clinical observations. Recommendations usually comprise non-pharmacologic strategies, such as increasing dietary fibre and fluid intake, which are, however, very rarely sufficient for constipation control in opioid related constipation.

A variety of pharmacologic treatments representing the whole range of different substance classes in the treatment of obstipation is recommended. However, treatment failure appears to be common, and rescue medication, such as enemas and other measures (including digital removal of faeces) have to be used.

Considering that the activation of  $\mu$ -opioid receptors in the gastro-intestinal tract is responsible for inhibition of gut motility, whereas receptors in the central nervous system mediate the analgesic action of opioid, the use of peripheral  $\mu$ -opioid receptor antagonist could be of benefit to the patients.

Wyeth Europa Limited submitted through the Centralised Procedure (*Art. 3 (2) (a)*), a “stand-alone” application for methylnaltrexone, a new chemical entity for the following claimed indication: “treatment of opioid induced constipation in patients with advanced illness”.

RELISTOR (INN: methylnaltrexone bromide) is a quaternary derivative of the  $\mu$ -opioid antagonist, naltrexone. Whereas naltrexone is used to counteract the CNS related effects of opioid treatment (including overdose), RELISTOR was designed to potentially block the undesired peripheral side effects of opioids without interfering the central analgesic effects.

The application is for an aqueous solution for injection administered subcutaneously containing 12mg/0.6ml per vial (equivalent to 20mg/ml) of methylnaltrexone bromide.

The product is to be administered with daily doses of 8 mg or 12 mg according to body weight (threshold: 61kg), by means of a single injection which should not be exceeded on a daily basis and which should be administered on an “as needed” basis on top of usual laxative treatment.

A comparable treatment has not been approved within the EU via centralised procedure. However, several products have been approved (nationally) with the  $\mu$ -antagonist naloxone in oral fixed combination products (e.g. tilidin/naloxone and oxycodone/naloxone), meant to reduce opioid induced side effects, especially opioid induced constipation.

No regulatory guidance is available in the European Union (EU) or in the United States (US) concerning the clinical development of products intended for use in opioid induced constipation.

The applicant did not request central Scientific Advice from the Scientific Advice Working Party for the non-clinical or clinical aspects of the development programme in the claimed indication. However, Scientific Advice was requested for the overall pharmaceutical part of the development, and for the clinical development in the indication “post-operative ileus”. In addition, meetings with several European National Competent Authorities (i.e. BfArM, Germany, the MHRA, UK, the AFSSAPS, France, and the MPA, Sweden) and with the FDA were conducted between 2003 and 2007 in the indication relating to this application.

## 2.2 Quality aspects

### Introduction

RELISTOR is a solution for injection containing 12 mg/0.6 mL of methylnaltrexone bromide (MNTX) per vial (equivalent to 20mg/mL) for subcutaneous administration. An overfill of 0.2mL is used in order to provide a withdrawable volume of 0.6mL. RELISTOR solution for injection is a clear solution, colourless to pale-yellow, essentially free from visible particulates supplied in clear Type I flint glass vial, gray butyl rubber stopper and aluminium overseal with flip off-cap.

The excipients used in the preparation of RELISTOR are sodium chloride, sodium calcium edetate, glycine hydrochloride, hydrochloric acid (to adjust pH), sodium hydroxide (to adjust pH) and water for injections.

### Active Substance

Methylnaltrexone bromide is a new chemical entity designated as (*R*)-*N*-(cyclopropylmethyl) noroxymorphone methobromide. The structure of MNTX is shown in Figure 1.

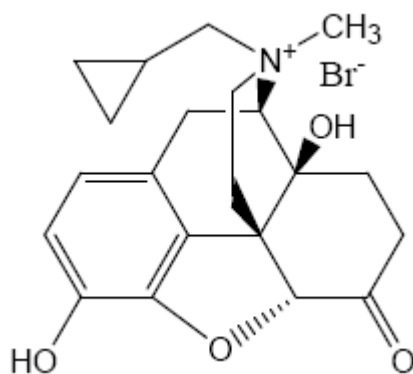


Figure 1: Chemical structure of MNTX

Methylnaltrexone bromide is a quaternary derivative of the opioid antagonist naltrexone. The addition of a methyl group resulted in a compound with greater polarity and lower lipid solubility, with reduced permeation through the blood-brain barrier and consequently, restricted access to the brain. The Active Substance Master File (ASMF) procedure was followed for the active substance.

Methylnaltrexone bromide is a white to off-white crystalline powder, soluble in water, non-hygroscopic, with a melting point of 251°C and a pH of approximately 4.6. Its octanol/water partition coefficient (log P) is of -1.12.

- **Manufacture**

MTNX is manufactured by a synthetic process. Details on the manufacturing process, control of materials, critical steps, process controls, and process validation were provided in the restricted part of the Active Substance Master File.

The structure of MNTX has been confirmed by FTIR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and MS. The NMR results confirmed the R configuration for the quaternary nitrogen. Particle size distribution was analysed by laser diffraction and polymorphism was investigated by X-ray powder diffraction.

- **Specification**

The active substance specifications include tests for appearance, identification (IR and HPLC), assay (HPLC), pH, water content (Karl Fischer), residue on ignition, loss on drying, heavy metals, specific rotation, bromide content, residual solvents (GC and HPLC), related substances (HPLC), microbial limits and bacterial endotoxins.

The IR method was validated for specificity. The HPLC and GC methods were validated for specificity, linearity, accuracy, precision, limit of detection and limit of quantitation. No validation was performed for the methods described in the PhEur.

Data was provided on 16 batches representative of the commercial manufacturing process. All the batch data complied with the specifications of the active substance. The results demonstrated that the active substance can be consistently manufactured by the proposed manufacturing process.

- **Stability**

Stability studies were performed on several commercial size batches of MNTX stored in the proposed packaging at accelerated conditions (40°C/75% RH) for up to six months and long term conditions (25°C/60% RH) for up to four years. The results support the proposed re-test period.

## **Medicinal Product**

- **Pharmaceutical Development**

A solution for injection for subcutaneous use was chosen as the pharmaceutical form, since it is most favourable to the patient's needs.

The aim of the pharmaceutical development was to develop a formulation that could be stored at room temperature. This was achieved by optimizing primary packaging and the formulation.

Aseptic processing and sterile filtration was chosen as the preferred method of sterilisation.

- **Adventitious Agents**

None of the excipients used in the formulation of MNTX solution for injection are of human or animal origin.

- **Manufacture of the Product**

A conventional manufacturing process was used, consisting of compounding, sterile filtration and aseptic processing.

There are several in-process controls such as the determination of the pH prior to the addition of hydrochloric acid and sodium hydroxide, determination of the bioburden prior to filtration, testing of the integrity of the sterilising filter pre and post filtration and check of the fill weight at startup and throughout the filling operation.

The manufacturing process and in-process controls were adequately described and validated in line with ICH guidelines.

Batch analysis data was provided on three batches. The data confirmed that the MNTX solution for injection can be manufactured reproducibly according to the finished product specifications.

- **Product Specification**

The specifications for MNTX solution for injection include tests for appearance and description (visual inspection), identification of MNTX (HPLC and UV), identification and assay of sodium calcium edetate (HPLC), assay (HPLC), impurities (HPLC), pH, volume in container, particulate matter, bacterial endotoxins, sterility and osmolality.

All methods have been satisfactory validated. The HPLC methods have been validated for specificity, linearity, precision, accuracy, robustness and solution stability. The endotoxins and sterility were also validated for MNTX solution for injection.

- **Stability of the Product**

Stability data was provided on three commercial scale batches manufactured by the proposed manufacturing site for the finished product. The batches were stored at 25°C/60% RH (long term conditions), 30°C/75% RH (intermediate conditions) for 12 months and at 40°C/75% RH (accelerated conditions) for 6 months, in the proposed container closure system. The parameters assessed were appearance and description, strength, purity and related substances, content of sodium calcium edetate and pH. The results in all studies complied with the product specifications in all batches.

Photostability studies were performed on one batch of MNTX solution for injection according to ICH option 2 light conditions on both packaged and exposed finished product. The results showed that the product is highly sensitive to light exposure, but stable when protected from light in the secondary packaging.

In conclusion, the stability results support the shelf life and storage conditions as described in the SPC.

## **Discussion on chemical, pharmaceutical and biological aspects**

The finished product was developed as a solution for injection for subcutaneous use. The aim of the pharmaceutical development was to obtain a stable product at room temperature. This was achieved by optimizing the primary packaging and the formulation. A conventional manufacturing process was used, consisting of compounding, sterile filtration and aseptic processing.

At the time of the CHMP opinion, there were minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

### **2.3 Non-clinical aspects**

#### **Introduction**

MNTX has been used as an investigational drug in the scientific community for far more than 20 years. Besides one receptor screen study, the safety pharmacology studies and the toxicity studies, all pharmacology data were not based on Company-initiated studies but were retrieved from published papers.

Preclinical safety studies and the majority of the toxicity and pharmacokinetics studies were performed according to GLP standards. Data described in the sections on primary and secondary pharmacodynamics and on pharmacodynamic drug interactions were mainly derived from published literature and did not meet GLP-standards.

#### **Pharmacology**

- **Primary pharmacodynamics (*in vitro/in vivo*)**

MNTX acts as an antagonist preferentially at the mu-opioid receptor ( $K_i=28$  nM), exhibits less potency at the kappa-receptor and shows no action at the delta-opioid receptor or at any other receptor investigated in a broad screen. The methylation in MNTX causes greater polarity and lower lipid solubility of the molecule, and hence, MNTX is restricted from crossing the blood-brain barrier in animals and in humans at clinically relevant doses. MNTX is intended for application via the s.c. route, and therefore its action is expected to be restricted to the periphery.

In several species it has been demonstrated *ex vivo* (guinea pig, horse, human) and *in vivo* (mouse, rat, dog, horse) that MNTX effectively antagonises (in case of the *in vivo* data after peripheral administration as intended for clinical use) the opioid-induced inhibition of gastrointestinal function. Typical effective s.c. doses in these studies were about 1 to 30mg/kg. Opioid-induced analgesia, a centrally mediated effect, was generally not affected after peripheral MNTX administration in several species (mouse, rat, guinea pig). In the mouse and in the rat opioid-induced analgesia was diminished at MNTX concentrations of about 100-fold the human dose. This is in line with the concept of demethylation of MNTX to the centrally easily passable NTX in rodents, a metabolic reaction shown to be essentially absent in humans.

The R-isomer of MNTX has been developed for use, due to its mu-opioid receptor antagonism, as opposed to the weak agonist effect of the S-isomer. Chiral conversion was considered unlikely to occur as the quaternary nitrogen of MNTX is constrained in a cyclic system and lacks an unshared pair of electrons. Consequently, chiral conversion will have no implications for efficacy and safety of the product.

MNTX administered peripherally was shown to be devoid of withdrawal-precipitating actions in morphine (MO)-dependent in dogs (50 mg/kg s.c.) and rhesus monkeys (32 mg/kg s.c.), and was ineffective in blocking discriminative effects in monkeys (10 mg/kg i.m.) trained to discriminate the opioid etorphine from saline. In line with the known metabolic conversion of MNTX to NTX in rodents, MNTX precipitated only very weak withdrawal-signs in MO-dependent mice.

Peripherally administered MNTX was active in counteracting MO-induced emesis in dogs and pica-behaviour (a phenomenon consisting of consumption of non-nutritive substances) in rats, a species which lacks the motor response to emetic stimuli.

- Secondary pharmacodynamics

The reported secondary pharmacology studies supported the opioid-antagonist activity of MNTX, with central effects generally occurring only when MNTX is administered intracerebroventricularly. Other routes of administration appeared to restrict the action to peripheral sites, although some reversal of morphine-induced analgesia was seen in mice and rats, suggesting that either small quantities of MNTX can cross the blood-brain barrier in these species, or that MNTX is converted to naltrexone, which is able to enter the CNS.

- Safety pharmacology

The applicant performed 1 study to investigate neuropharmacological effects in mice, a total of 7 studies investigating cardiovascular effects (including 2 studies employing cloned hERG channels and 2 studies measuring effects on action potentials in isolated rabbit and dog cardiac Purkinje fibers), 1 gastrointestinal propulsion assay in rats, 1 study investigating pulmonary effects in guinea pigs and 1 study on renal effects in rats.

MNTX had no effect on CNS in mice, on the GI system in rats or on the respiratory system in guinea pigs when administered i.v. at doses of 1, 4 or 16mg/kg. Intravenous doses of 1, 5, or 20mg/kg had no effect on renal function in rats.

Electrophysiological hERG channel recordings, *in-vitro* APD measurements of rabbit cardiac Purkinje fibers and ECG tracings in guinea pigs indicated a very low torsadogenic potential of MNTX, whereas APD prolongation in canine cardiac Purkinje fibers was observed at concentrations ( $\geq 1 \mu\text{M}$ ) not markedly higher than the therapeutically intended effective free serum concentration in humans (about  $0.28 \mu\text{M}$ ). No explanation for the MNTX-induced APD prolongation in the canine Purkinje fiber was provided. Effects on  $I_{Kr}$ ,  $I_{Ks}$ , and  $I_{Na}$  did not appear to be involved in the observed APD prolongation. Hence, the effects of MNTX were further investigated in humans (see the “Clinical aspects” section 3.4).

- Pharmacodynamic drug interactions

Preclinical studies investigating pharmacodynamic drug interactions with concurrently administered laxatives, a combination which is stated in the intended indication, were not performed in animals. However, in the main clinical studies nearly all patients were administered conventional laxatives

concurrently with MNTX. As a result, there was no need for further preclinical animal studies investigating pharmacodynamic interactions between conventional laxatives and MNTX.

Taken together the preclinical data on pharmacology supported the use of MNTX in the intended indication in humans.

### **Pharmacokinetics**

The pharmacokinetics of MNTX was studied in mice, rats, and dogs after subcutaneous, oral and intravenous dosing. Distribution was investigated in rats and rabbits after epidural (rabbits), intravenous (rats), and intraperitoneal (rats) dosing. Protein binding was studied in rats, dogs, and human plasma. Metabolism was studied in rats (s.c., i.v., and oral), mice (oral), dogs (oral, i.v.) and in various hepatic preparations. Inhibitory and induction effects on cytochrom isoforms was investigated *in vitro* in human liver microsomes and cultured hepatocytes. Excretion was studied *in vivo* in rats, mice, and dogs and isolated perfused kidneys and in human transport proteins expressing oocytes. Biliary excretion was investigated in bile duct-cannulated rats.

### **Methods of analysis**

MNTX was detected and quantified by High Pressure Liquid Chromatography (HPLC) (in rat brain and serum) with electrochemical detection, or by liquid chromatography-tandem-mass spectrometry (LC/MS/MS) (in all other cases).

- **Absorption**

MNTX was administered to male rats intravenously, subcutaneously and via gavage. MNTX showed a moderate to high plasma clearance compared to liver blood flow and a moderate volume of distribution compared to body water. Bioavailability was essentially complete after s.c. dosing and very low (<1%) after oral administration. This was consistent with results obtained in Caco-2 cells, which predicted a low GI uptake. The half-life ( $t_{1/2}$ ) ranged between 6 to 18 hours (i.v.), or 6 to 10 hours (s.c.), and 2 to 16 hours (oral).

- **Distribution**

The tissue distribution study after i.v. administration in rats showed that the highest concentration of MNTX in tissue was reached within 1 hour (in the small intestine, liver and kidney with the highest, and in the brain with the lowest concentration). Afterwards the concentration in most tissues decreased, although the tissue-to-plasma ratios increased for 12 hours, indicating much faster plasma than tissue clearance. High tissue-to-plasma ratios were observed in thyroid, brown fat, heart, testes, eyes and peritoneal fat after 24 and 120 hours. The studies on brain uptake showed a marginal uptake of MNTX into the brain of mammals, (as already shown for other tissues) with a slower clearance compared to plasma. Metabolites including naltrexone were detected in the brain.

Protein binding of several concentrations of MNTX was estimated in rats, dogs and human plasma and ranged between 0.4 to 13.3 % indicating minimal binding of MNTX to plasma proteins.

- **Metabolism (*in vitro/in vivo*)**

*In vivo* metabolism of MNTX was investigated in rats, dogs, mice, and human. In rats, unchanged MNTX was the main compound in plasma and MNTX glucuronide and sulphate were the main metabolites after IV and solely the glucuronide after oral administration. In mice, MNTX was found to be the main compound in plasma after oral administration. Several minor metabolites including MNTX glucuronide were identified. In humans MNTX was moderately metabolised with MNTX sulphate (4.1%) and methyl-6-naltrexol isomers (17.7 % of total MNTX) being the major metabolites. Thus, demethylation of MNTX to naltrexone is not a significant metabolic pathway in humans.

*In vitro* metabolism studies in several systems indicated MNTX metabolism by hydroxylation, glucuronidation, methylation and glutathione (only in rats) conjugation. MNTX was moderately metabolised in mice and rats, minimally in dogs and in human hepatocyte systems. MNTX was stable in human and rat liver microsome systems, whereas a minimal metabolism was detected in dogs. In humans, sulphation and reduction to methyl-6-naltrexol isomers were the main pathways. In all species investigated metabolism was limited, with the main compound in excreta being MNTX. Rat and dog were considered to be appropriate species for the toxicology studies. N-demethylation to

naltrexone occurred to a limited extent, but was greater in rats and mice than in dogs, and was negligible in humans.

MNTX was stable when incubated with human CYP isoforms. With the exception of CYP2D6 (Ki 7.9 µmol/l), no competitive inhibition of the CYP enzymes was found. It was concluded that it is not likely that a clinically relevant inhibition may appear after regular SC doses of MNTX. MNTX did not induce any CYP isoforms in humans. Test systems for glucuronidation showed similar effects as *in vivo* experiments.

- Excretion

MNTX was excreted via faeces and urine in all species after oral and systemic application. Studies in bile duct-cannulated animals as well as studies with intravenous administration allowed the conclusion that MNTX is excreted biliary and via secretion into the gastro intestinal tract.

MNTX is actively secreted into the urine. In line with the results from several clinical studies, the clearance was higher than the glomerular filtration rate in externally perfused kidneys. It was shown that MNTX is a substrate of the human organic cation transporter.

- Pharmacokinetic drug interactions

Pharmacokinetic drug interactions were investigated with cimetidine, ranitidine, procainamide, and morphine. Although MNTX was a relevant substrate of CYP2D6 and the human organic cation transporter, no clinical relevant interactions were assumed.

### **Other Pharmacokinetic Studies**

- Placental Transfer and Lactal Excretion

Following a single subcutaneous administration of 10 mg/kg [<sup>3</sup>H]-MNTX to pregnant rats, tissue distribution in the dam and fetus was investigated up to 8 hours post-dose. [<sup>3</sup>H]-MNTX-derived radioactivity was readily distributed to the fetus. The fetal-to-maternal plasma radioactivity concentration ratio was 0.1 at the t<sub>max</sub> (1 hour) in fetuses, which increased to 0.8 at the last sampling time point at 8 hours. The data suggested that [<sup>3</sup>H]-MNTX and possible metabolites crossed the placenta and were cleared from fetal plasma at a lower rate than from maternal plasma.

Similarly, milk transfer of MNTX was shown in lactating rats. Lactating female rats were treated with a single subcutaneous injection of 10 mg/kg [<sup>3</sup>H]-MNTX at day 10 postpartum. Milk was collected at different time-points up to 8 hours post-dose. Plasma and milk concentrations of [<sup>3</sup>H]-MNTX were determined. The milk-to-maternal plasma concentration ratios at 0.5 and 8 hours after dosing were 0.1 and 24.0, respectively. These data indicated that [<sup>3</sup>H]-MNTX-derived radioactivity was excreted into the milk of lactating rats; as a result, exposure of pups to the drug through nursing cannot be excluded.

### **Toxicology**

- Single dose toxicity

Single dose toxicity studies are summarised in the table below:

<b>Study ID</b>	<b>Species/ Sex/Number/ Group</b>	<b>Dose (mg/kg) /Route</b>	<b>Approx. lethal dose / observed max non-lethal dose</b>
RPT-63484	Rat/ 1/sex/group	20, 30, 40, 50, 80, 120, 200, 400, 500 /SC	>500mg/kg / 500mg/kg
RPT-64345	Rat / 3 or 4/sex/group	120, 400 (in saline, +/- 1.2 or 4mg/ml Ca EDTA) /SC	>400mg/kg / 400mg/kg
RPT-65328	Rat / 5/sex/group	40, 120 (in saline +/- 0.4mg/ml Ca EDTA) /SC	>120mg/kg / 120mg/kg

Study ID	Species/ Sex/Number/ Group	Dose (mg/kg) /Route	Approx. lethal dose / observed max non-lethal dose
RPT-66391	Rabbit/ M/ 3/group	5, 20, 35mg in 6 different formulations / SC	> 35mg / 35mg

**Table 1:** Single dose toxicity studies.

General signs of toxicity were abnormal gait and stance, low carriage, body tremors and labored respiration. The single dose toxicity studies exhibited a relatively low acute toxicity.

- Repeat dose toxicity (with toxicokinetics)

Repeated dose toxicity studies are summarised in the table below:

Study ID	Species/Sex/ Number/Group	Dose (mg/kg/day) /Route	Duration	NOEL/ NOAEL (mg/kg/day)
RPT-63483	Rat/ 3/sex/group	200 (2ml/kg of 100mg/ml solution) /SC	4 days	Not established
RPT-63501	Mouse / 20/sex/group	80, 400, 2000/1500 / oral (gavage)	90 days	80
RPT-64868	Rat / 10/sex/group	5, 15 (in saline or saline + 0.4mg/ml CaEDTA) / IV	14 days	5
RPT-63490	Rat / 15/sex/group	1, 5, 20 / IV	90 days	5
RPT-63498	Rat / 15/sex/group	80, 400, 2000 / oral	28 days	2000
RPT-63662	Rat / 20/sex/group	100, 1000/500, 3000/2000/1000 / oral	26 weeks	100
RPT-63485	Dog / 4/sex/group	5, 20, 40 (2.5, 10, 20 BID) / IV	14 days	40
RPT-63491	Dog / 4/sex/group	1, 5, 25/20 / IV	90 days	5
RPT-63499	Dog / 4/sex/group	60, 300, 1500/1000/750 / oral gavage	28 days	60
RPT-63502	Dog / 4/sex/group	20, 60, 180/225/250 / oral gavage	39 weeks	

**Table 2:** Repeat-dose toxicity studies.

Repeat-dose toxicity studies were performed in mice, rats, and dogs by oral or intravenous administration. Although MNTX is to be applied subcutaneously, the applicant's approach was considered acceptable, since the pharmacokinetic studies showed similar exposures after subcutaneous (in human 80% of the AUC of the intravenous application) and intravenous

administration in animals as well as in human volunteers. As shown in the toxicokinetic parts of repeat-dose toxicity studies, the animals were sufficiently exposed to MNTX. Additionally, no significant metabolic differences were found between the different administration routes. It is noteworthy that the solely human metabolite M4 (methyl-6 $\alpha$ -naltrexole) was not tested in animal experiments.

The main clinical signs of MNTX exposure at high doses were tremors, convulsion, decreased activity, abnormal stance and gait, and prostration in rats as well as in dogs. In addition, in dogs also ptosis, bloodshot eyes, protruding nictitating membranes, dilated pupils and absence of menstrual cycling were apparent.

Adverse CNS-related clinical signs occurred in rats after subcutaneous doses above 200 mg/kg/day and after intravenous dosages above 20 mg/kg/day. In dogs, adverse CNS-related clinical signs occurred after intravenous dosages of 20 mg/kg/day and at oral exposure above 180 mg/kg/day. These results supported the finding from the pharmacokinetic studies that limited amounts of MNTX may cross the blood-brain barrier of animals at high plasma concentrations.

Very high dose of MNTX ( $\geq 300$  mg/kg/day in dogs and  $\geq 500$  mg/kg/day in rats) seemed to influence hemodynamic parameters (mainly blood pressure).

No changes of macroscopic, microscopic and clinical chemistry parameters were described.

The toxicokinetic data provided were compromised by the absence of a calculation of the safety margins for the individual studies. Only in the non-clinical overview some estimates could be found. The whole body of data showed that the animals were sufficiently exposed to MNTX in the toxicity studies. With the exception of the 26 week oral rat study the calculated safety margins were considered sufficiently high to support the marketing authorisation. It remained a matter of debate if an accumulation of MNTX may be apparent after high dosages and if a dose-dependent linear increase of the AUC has to be assumed. Under consideration of the clinical use of MNTX (on demand) and the stipulated dosage (0.15 or 30 mg/kg) the clinical relevance was considered to be poor.

- Genotoxicity *in vitro* and *in vivo* (with toxicokinetics)

Genotoxicity was addressed extensively in a battery of tests (according to ICH S2B) containing bacterial reverse mutation assay, *in vitro* mammalian cell mutation assay, two *in vitro* mammalian cell chromosomal aberration assays and two *in vivo* mouse micronucleus assays with intraperitoneal and subcutaneous application. The studies did not provide any evidence for clinically relevant genotoxic potential of methylnaltrexone (MNTX).

- Carcinogenicity (with toxicokinetics)

No carcinogenicity studies were provided. This was justified based on the limited life expectancy of the patient population and the absence of genotoxic potential.

- Reproductive and developmental studies

MNTX was evaluated in a rat fertility study, in embryo/fetal development studies in rats and rabbits and in a pre/postnatal study in rats with subcutaneous or intravenous administration of the drug. All studies were GLP compliant. Milk and placental transfer of MNTX were shown after subcutaneous administration in the rat.

In the fertility study, MNTX impaired fertility in the high dose group rats. The NOAEL for fertility was therefore established at 25 mg/kg/day given subcutaneously. Studies on embryo-fetal development were conducted with intravenous application of MNTX to the rat and the rabbit. MNTX did not show any developmental toxicity (feto-/embryotoxicity, teratogenic effects). The developmental NOAEL was considered to be 25 mg/kg/day for the rat and 16 mg/kg/day for the rabbit. Exposure of pregnant animals to MNTX was shown in single dose toxicokinetic studies. In the study on pre-/postnatal development in the rat, a reduction in pup weight was observed in the high dose group. Therefore, the NOAEL for pre/postnatal development was established at 25 mg/kg/day, the next lowest dose. Concurrently with the pre/postnatal study, pharmacokinetic parameters were obtained. A safety margin of 38 could be calculated at the NOAEL for a human dose of 0.15 mg/kg and of 17 for a human dose of 0.30 mg/kg (based on AUC).

- Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

Juvenile toxicity studies were not performed.

- Local tolerance

Specific local tolerance studies were not performed. However, local effects in the various toxicity studies were evaluated. Even though the local tolerance of the final formulation was not tested in animals, very similar solutions were used in the non-clinical studies. In these studies no adverse injection site changes were observed. Additionally, the clinical safety data did not show an increased number of adverse events of skin and subcutaneous tissue.

- Other toxicity studies

Impurities were found to be limited in the drug substance and finished product, in line with ICH guidelines.

The spectrum of MNTX exhibited no significant absorbance between 290 and 700 nm. However a minor peak was detected at 281.9 nm, which was considered to be without clinical relevance. The applicant submitted a study in pigmented rats, whereby no distribution into the skin or eyes was detected, irrespective from the fact that MNTX distributed to the eye in one further study. Since no absorption in the relevant range was observed, further photo-safety testing was not required.

### **Ecotoxicity/environmental risk assessment**

The Applicant provided epidemiological data from the WHO Statistical Information System (WHOSIS) and publications for the estimation of number of patients expected to be treated with methylnaltrexone bromide. The data resulted in a predicted environmental concentration in surfacewater (PEC<sub>sw</sub>) for MNTX in the applied indication (i.e. treatment of opioid-induced constipation in patients who have advanced illness) below the action limit of 10ng/l triggering a phase II environmental risk assessment. The final ERA submitted was therefore deemed acceptable.

## **2.4 Clinical aspects**

### **Introduction**

The clinical programme for RELISTOR consists of six phase I, one phase II and two phase III studies, performed to establish the clinical pharmacokinetics and the clinical safety and efficacy of s.c. methylnaltrexone in the palliative care setting.

The approved indication for RELISTOR is “Treatment of opioid-induced constipation in advanced illness patients who are receiving palliative care when response to usual laxative therapy has not been sufficient.”

### **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.

### **Pharmacokinetics**

The documentation of the clinical pharmacokinetics of methylnaltrexone encompasses six phase I studies (MNTX 102; MNTX 103; MNTX 1105-1108).

Studies MNTX 103, MNTX 1106, and 3200K1-103-US related to understanding the absorption, bioavailability, and pharmacokinetic linearity (dose-proportionality) of the compound given as s.c. injection. Of these, MNTX 1106 was a pharmacodynamic safety study designed to document the effects of the substance on QT prolongation. However, because of the different dose levels investigated, and the high number of subjects involved, it was used to document dose-proportionality.

Study MTNX 102 was a mass balance study with i.v. administration of the compound in order to determine the basic PK characteristics.

Studies MNTX 1105 and MNTX 1107 documented respectively the PK of MOA-728 in patients with renal or hepatic impairment, and study MNTX 1108 investigated the potential interaction with a typical CYP 450 2D6 substrate (dextrometorphan).

The applicant submitted 2 further studies evaluating certain aspects of the PK of the substance (MNTX 1303 and MNTX 1304).

### Methods

Part of the methods used for the quantification of the active substance MTNX in human plasma and urine were published at an early stage of the development; others were developed in support of this submission.

Human plasma and urine concentrations of MNTX and human urine concentrations of dextrometorphan and dextrorphan were determined by LC/MS/MS assay methods, which were properly validated and met the usual acceptance requirements.

- *Absorption*

MNTX is absorbed rapidly following s.c. administration, with peak plasma concentrations achieved at approximately 0.5 hours.  $C_{max}$  and AUC increase dose proportionally over the therapeutic dose range in healthy volunteers (Study MNTX 103). The terminal half life ranges from 6 to 9 hours and appears to be independent of dose and route of administration. (See table below).

Metric	IV MNTX	SC MNTX	SC MNTX	SC MNTX
	0.30 mg/kg	0.10 mg/kg	0.30 mg/kg	0.45 mg/kg
$C_{max}$ (ng/mL)	1006 (190)	47.5 (12.3)	197.0 (47.0)	317.0 (82.0)
AUC <sub>t</sub> (ng/mL*h)	378.6 (52.3)	72.1 (10.4)	301.9 (42.5)	544.0 (33.9)
AUC <sub>∞</sub> (ng/mL*h)	379.8 (52.9)	73.3 (10.6)	303.2 (43.1)	545.7 (34.6)
$t_{max}$ (h)	0.06 (0.01)	0.45 (0.21)	0.30 (0.11)	0.45 (0.11)
$t_{1/2}$ (h)	7.81(1.17)	6.14 (0.88)	8.04 (1.67)	8.83 (0.85)
F		0.60 (0.07)	0.82 (0.08)	0.99 (0.14)
$V_{area}$ (L/Kg)	9.05 (1.81)			
$V_{area}/F$ (L/Kg)		12.3 (2.1)	11.70 (2.90)	10.5 (1.1)
$V_{ss}$ (L/Kg)	1.96 (0.60)			
Cl (L/hr/kg)	0.80 (0.11)			
Cl/F (L/hr/kg)		1.39 (0.21)	1.00 (0.14)	0.83 (0.05)
$f_R$ (%)	43.5 (7.1)	25.6 (4.0)	24.3 (4.2)	50.5 (4.1)
Cl <sub>R</sub> (mL/min)	401.6 (88.6)	397.5 (84.0)	270.6 (44.8)	469.5 (59.3)

**Table 3:** Pharmacokinetics estimated according to plasma concentration time course and cumulative urine data in study MNTX 103

An absolute bioavailability of 82% was measured comparing the i.v. and s.c. routes of administration of the compound (at a dose of 0.30 mg/kg, comparing AUC).

Different formulations were used in the early development, in the phase III trials and for marketing.

A bioequivalence study for the comparison of the formulation G (stored at 25° C and intended to be the marketed formulation) and the formulation D (stored a 2-8°C) was performed (Study 3200K1-103-US), which included 28 healthy male and female subjects, of whom 27 completed the study.

The mean plasma MOA-728 concentration versus time profiles of the current (formulation D) and the new (formulation G) s.c. formulations in the 27 healthy subjects at a dose of 0.15 mg/kg appeared to be identical. Moreover, the 90% CI's of the ratios of the  $C_{max}$  and AUC values were clearly within the bioequivalence range of 0.80 to 1.25 for all the different formulations.

Since the compound is to be given as a subcutaneous injection, the influence of food intake was not investigated.

- *Distribution*

The PK distribution was mainly characterised in study MNTX 102, which was performed with i.v. dosing and which included 6 healthy male volunteers. A relatively large volume of distribution ( $V_{\text{area}}=7.92 \pm 1.54$  l/kg) was found, suggesting that MNTX is distributed extensively outside the central compartment. The distribution after repeated i.v. dosing was also investigated in the interaction study MNTX 1108, where the distribution at steady state was determined with a mean  $V_{\text{ss}}$  of  $1.1 \pm 0.21$  l/kg, indicating a more moderate distribution into extravascular spaces.

A minimal distribution into blood cells was observed, as the total radioactivity in plasma was roughly twice than the one in the whole blood. MNTX resulted minimally bound to human plasma proteins as determined by equilibrium analysis. The binding of MNTX to human plasma protein ranged from 11.0% to 15.3% (at the concentrations of 0.2 and 2.0  $\mu\text{g/ml}$ ).

- *Elimination and metabolism*

The main elimination characteristics were determined in the mass balance study MNTX 102. The mean total percent of administered radioactivity recovered was 70.9%, with 53.6% in urine, and 17.3% in the faeces, predominantly within the first 24 hours in urine and within the first 48 hours in the faeces. The mean total percent of administered dose recovered in the urine was  $58.6 \pm 18.2$ .

Exhaled  $\text{CO}_2$  accounted for a negligible amount of radioactivity (collected in periodic samples of expired air over an 8-hour period). Renal excretion and gastrointestinal efflux/hepato-biliary secretion of unchanged drug appeared to be the major mechanisms of MNTX clearance.

The total clearance of MNTX amounted to  $10.5 \pm 1.5$  ml/min/kg, although the contribution of the renal clearance was only  $6.37 \pm 3.0$  ml/min/kg. Likewise, renal clearance exceeded creatinine clearance by up to 4-fold (Studies MNTX 102 and MNTX 103), confirming that selective tubular excretion (active renal secretion) occurred significantly. The total clearance after multiple doses (interaction study 1108) was  $11.11 \pm 1.87$  ml/min/kg.

Since MNTX is positively charged at any physiological pH, the process of its active renal secretion across the basolateral membranes of proximal tubule cells is likely to be mediated mainly by the organic cation transporters hOCT. Study MNTX 1304 evaluated the interaction between MNTX and the OCT transporters, whereby cimetidine (a well-known inhibitor of the OCT-1 transporter) was chosen as an appropriate comparator. Cimetidine was responsible for a limited increase of 10% of the plasma concentrations of MNTX, and this was deemed to be non-clinically relevant.

RELISTOR resulted metabolically stable both in human and rat liver microsomes, whereas substantial decreases of RELISTOR were seen in dog microsomes, indicating time and dose dependant significant metabolism. The complete metabolic profiling (*in vivo*) identified the following metabolites: M1 (Methyl-6-naltrexol Sulfate), M2 (Methylnaltrexone Sulfate), M3 (Dihydroxy-methyl-6-naltrexol), M4 (Methyl-6-naltrexol Isomer) and M5 (Methyl-6-naltrexol Isomer).

Overall, only limited biotransformation of MNTX was observed in humans after i.v. administration, as metabolism contributed for less than 10% of the total MNTX clearance.

The mean plasma  $\text{AUC}_{12}$  ratio of unchanged MNTX to total radioactivity was reported to be 0.59, potentially suggesting pharmacokinetic differences between parent drug and metabolites.

Methylnaltrexone is a chiral substance; the drug substance, however, consists of the R-isomer.

- *Pharmacokinetics of metabolites*

Study MNTX-102 revealed that the metabolites PK profile appear to be different from the one of the mother compound. However, the PK of the metabolites was not investigated further. Given the low plasma levels of the metabolites, this was considered acceptable.

- *Consequences of possible genetic polymorphism*

As the substance was only metabolised in negligible amounts, consequences of any genetic polymorphism (relating to known drug metabolising enzyme genes) were not expected. Genetic

polymorphism of the OCT-1 transporter gene and genetic polymorphism of the opioid receptor system were not established.

- *Dose proportionality and time dependencies*

Linearity was investigated in study MNTX 103 and in the “definitive QTc-study” MNTX 1106, employing single doses of s.c. MNTX at the dose levels of 0.15 mg/kg, 0.30 mg/kg, and 0.5 mg/kg in 207 healthy adult subjects. Blood sampling was performed simultaneously with ECG tracing at different time-points (up to 24 hours after dosing). A combined analysis of the relevant PK studies (MNTX 103, MNTX 1105, MNTX 1106, and MNTX 1107) was performed, collecting data from a total of 140 healthy volunteers.

Despite deviations observed for the 0.10 and the 0.45 mg/kg dose levels, overall a clear dose linearity could be concluded. MNTX administered at a dose of 0.45 mg/kg as a 20 minute i.v.-infusion every 6 hours for 5 doses resulted in a minimal accumulation factor (R) of 1.19 (Study MNTX 1108). An accumulation factor of R=1.07 was determined in the QT study MNTX 1106.

It was recognised that the compound is to be given on an “on demand” basis, and not more than one dose (of 8 mg or 12 mg) is proposed to be given within 24 hours.

Additional data were presented confirming that no or minimal accumulation should be anticipated for repeated administration of MNTX with a dosing interval of 6 hours or longer (Studies MNTX 1303 and MNTX 1108). Accumulation was also shown to be minimal in the steady-state PK profiles of s.c. MNTX simulated by superposition of PK data following s.c. single doses of 0.30 mg/kg (Study MNTX 1106).

- *Intra- and inter-individual variability*

Intra-subject coefficients of variation for  $C_{max}$  and AUC at 13.4% and 9.2% were estimated (study MNTX-103), revealing limited variation in plasma levels within and between subjects. Additional data were presented on the pharmacokinetic metrics of MNTX following s.c. doses (MNTX 1106), indicating that variability for the relevant parameters (AUC<sub>24</sub> and  $C_{max}$ ) was not of concern.

- *Pharmacokinetics in target population*

No PK studies were performed in the target population.

### **Special populations**

- *Impaired renal function*

The PK of MNTX in patients with mild, moderate, and severe renal impairment who did not require haemodialysis compared to healthy subjects was evaluated (Study MNTX 1105). The study enrolled 8 healthy subjects, matched to 3 groups of 8 patients each with mild, moderate, or severe renal impairment. Each subject or patient received a single s.c. dose of 0.3 mg/kg MNTX.

MNTX was rapidly absorbed after s.c. administration with mean  $t_{max}$  values not relevantly different between the groups (0.4 to 0.6 hours). The  $t_{1/2}$  increased from 13.4 hours to 19.6 hours with increasing severity of renal disease.  $C_{max}$  values displayed a relatively high variability but all in all suggesting a progressive increase with degree of renal impairment, however, with only the group with severe impairment showing increased values as compared to the healthy volunteers. Mean total exposure did however increase as a function of renal impairment severity. Likewise, decreases in the % of MNTX dose excreted in urine and in renal clearance were apparent with the increase in severity of renal impairment.

In conclusion, renal function impairment had a marked effect on the PK of MNTX. However, an 8- to 9-fold reduction of renal clearance resulted in only a 2-fold increase in total exposure. For comparison, the highest s.c. MNTX dose that was administered safely to healthy subjects (0.5 mg/kg) resulted in an exposure of  $582 \pm 111$  ng/ml x h (study MNTX 1006). Severe impairment resulted in an AUC that was 20% greater ( $AUC_{0-24}$   $739 \pm 66$  ng/ml x h) in study 1105. As a result, a dose adjustment is to be recommended for patients with severe renal impairment, and this is reflected in the SPC.

- *Impaired hepatic function*

The effect of impaired hepatic function on the PK of MNTX was studied in study 1107.

Rapid absorption with  $t_{max}$  values of <0.5 h occurred in all groups.  $t_{1/2}$  did not show a clear trend within the different groups (normal, mild and moderate hepatic function), suggesting that hepatic impairment did not have an effect on terminal half life. However, increased and relatively high variance was observed, especially in the moderately impaired group.

There was a trend for a slight increase of peak exposures with the degree of hepatic impairment. Mean total exposure, however, did again show no clear trend, with a lower total exposure in the mild impairment group, and a slightly increased exposure for the moderately impaired patients.

The fraction for renal excretion was consistent with previous findings for healthy subjects, but showed a decrease in the mildly and moderately impaired groups.

It was therefore concluded that hepatic status does not have a clinically significant impact on the plasma PK of MNTX, and no dose adjustment appears to be necessary for patients with mild or moderate impairment. However, a cautionary note for patients with severe impairment, which were not investigated, appears to be necessary. This is reflected in the SPC.

- *Gender*

The influence of gender on PK parameters was performed using a combined analysis of four studies (MNTX 1105-1107, and MNTX-103), including the data of a total of 140 healthy volunteers.

A significant difference in  $C_{max}$  (and MRT values) and in the quantity recovered unchanged in the urine (43% for females and 49% for males) was detected, however these differences were not considered clinically significant. Overall, the analysis of the PK parameters showed no relevant differences between the two genders.

- *Race*

Statistically significant differences were detected for  $t_{1/2}$  and V/F. However, clinical significance of these findings was denied. In conclusion, a clinical effect of race and ethnicity on the PK parameters (e.g. percent of dose eliminated in the urine) was not observed.

- *Weight*

Body weight was found to have a statistically significant effect on the following four metrics:  $AUC_{0-\infty}$ , Cl/F, and  $t_{max}$ . The effect was, however, not considered clinically relevant. The relation of AUC with body weight, showing relatively higher exposure at the upper end of the weight scale, was used to determine the fixed dosing schedule proposed for clinical use.

- *Justification of fixed dosing regimen:*

The vast majority (approx. 95%) of patients included in the clinical efficacy and safety programme were in the weight band of 38 – 114 kg for which the fixed dosing regimen (8 mg or 12 mg) is proposed.

Mean AUC estimates (0.15 mg/kg and 0.30 mg/kg) over a body weight range of 38 to 114 kg using the AUC body weight relation are shown below (**Table 4**):

Body Weight (kg)	0.15 mg/kg	0.30 mg/kg
38	139	277
68	179	357
114	240	480

The exposure at the higher end of these ranges is relatively high, and therefore a smaller weight-based dose could be given to these patients while maintaining a similar level of exposure.

The proposed fixed dosing regimen results in the following relative weight-based doses and predicted exposure (**Table 5**):

Body Weight (kg)	Dose (mg)	Dose (mg/kg)	AUC (ng·h/mL)
38-61	8	0.21-0.13	194-148
62-114	12	0.19-0.11	220-169

It was concluded from these data that the AUC obtained at doses of 8 and 12 mg for their respective weight bands are comparable to those obtained with the 0.15 mg/kg for the given population with body weights of 38 to 114 kg. In fact the predicted exposure seems to be relatively lower in the group with higher weights, and in the same range for the low(er) weight group.

- *Elderly*

The applicant performed a phase I PK study comparing the PK profile of MNTX in the elderly and non-elderly population (Study MNTX 1303). The study enrolled 14 (10 treated, 4 placebo) healthy young (18-45 year) subjects and 14 (10 treated, 4 placebo) healthy elderly (65 $\geq$  year) subjects. All subjects received MNTX 24 mg as a slow infusion over 20 minutes at day 1, followed by 17 doses between day 3 and day 7 every 6 hours.

The study revealed a somewhat slower clearance in the elderly (mean Cl = 70 L/h in the young, 56 L/h in the elderly). A little difference regarding C<sub>max</sub> of MNTX was also observed, whereas a larger and significant increase of 32.1% and 20.3% at day 1 and day 7 respectively was shown for AUC<sub>t</sub>. However, this change of clearance and AUC<sub>t</sub> in the elderly was considered to be not clinically relevant. In conclusion, age appeared to have a slight effect on the PK of MNTX, and this effect was considered to be in line with the reduction of renal clearance with age. The effect was, however, considered not clinically relevant and not sufficient in extent to require a modification in dose or dosing regimen.

- *Children*

MNTX was not investigated in children.

### **Pharmacokinetic interaction studies**

- *In vitro*

*In vitro* investigations revealed that MNTX did not induce CYP P450 enzymes and did not inhibit the CYP enzymes 1A2, 2A6, 2C9, 2C19 and 3A4 in human microsomes. However, a modest competitive inhibition of CYP 2D6 activity (IC<sub>50</sub> value = 15.92  $\mu$ M and K<sub>i</sub> = 7.93  $\mu$ M) was observed.

Further reassurance on CYP 2E1 enzymes was provided, as the applicant demonstrated that clinically significant MNTX drug-drug interactions based on induction of CYP 2E1 activity are unlikely (study RPT-72520), and that MNTX does not show *in vitro* inhibition of CYP 2E1 or CYP 2B6 activity at the highest concentration tested (100  $\mu$ M) (study RPT-71772).

- *In vivo*

A clinical interaction study (Study MNTX-1108), enrolling overall 54 subjects (45 receiving at least one dose of a study medication), was performed. 31 subjects were randomised to one of the four treatment groups and all of these completed the study. The endpoint for this study was the change in urine dextromethorphan/free dextrophan ratio for patients treated with either MNTX (two dose levels), paroxetine, or placebo.

A considerable change occurred in the ratio from baseline in the paroxetine group, whereas the changes in the other groups appeared to be negligible and in the range of placebo. This suggested an inhibitory effect of paroxetine 20 mg PO on CYP 2D6 activity. Overall, CYP 2D6 activity appeared not to be influenced to a clinically relevant extent, as even supra-therapeutic levels of MNTX did not influence the metabolic ratio of a typical 2D6 substrate. In conclusion, a clinically relevant interaction regarding the inhibition of CYP 2D6 with MNTX appeared to be highly unlikely.

### **Exposure relevant for safety evaluation**

S.c. methylalntrexone was investigated in 4 phase I studies (MNTX 103, MNTX 1105-1107), evaluating 269 subjects in total. The whole phase I programme also comprised data from 8 healthy adult volunteers included in the i.v. mass balance study MNTX-102, from 13 healthy volunteers receiving a single i.v. dose of 0.30 mg/dl in the Study MNTX-206, and from 16 healthy volunteers of which 8 each received i.v. (multiple dose) and s.c MNTX (single-dose) in the interaction study MNTX 1108. The studies which were filed at later time-points (MNTX 1303 and 1304) included 20 and 18 healthy volunteers). As a result, the total exposure to MNTX in phase I was 344.

## Pharmacodynamics

The pharmacodynamics (PD) in man was mainly investigated by the University of Chicago programme, for which several literature reports relating to human pharmacodynamics were reported. The further development on PD only included the QT-safety study and a study on the influence of MOA-728 on the reversal of opioid effects on the human urinary bladder.

- *Mechanism of action*

MNTX is a quaternary benzomorphan derivative that is a selective antagonist of opioid binding at  $\mu$ -receptors. *In vitro* studies showed that MNTX binds to human  $\mu$ -opioid receptors with an inhibition constant ( $K_i$ ) of 28 nM (equivalent to approximately 9.7 ng/ml). The substance is highly selective for the  $\mu$ -receptor, as it has a 8-fold less potency to  $\kappa$ -receptors and does not interact with  $\delta$ -receptors. A variety of other receptors were investigated which MNTX does not interact with.

In a variety of further pre-clinical investigations MNTX prevented morphine-induced inhibition of electrically induced stimulation of the gut in the guinea pig and isolated human small intestine. Selectivity for  $\mu$ -receptors was also shown in a gastric-brainstem preparation. The blocking of the slowing of GI transit time was shown in rats. In addition, attenuation of prostaglandin-induced diarrhoea was observed in mice and attenuation of morphine-induced inhibition of gut electrical activity in dogs. The compound was also shown to reverse opioid-induced emesis in dogs and to decrease morphine-induced kaolin intake in rats (as a model for emesis).

Further studies proved that administration of MNTX does not interfere with opioid analgesia at dosages that relieve opioid-induced GI side effects (mouse hot plate model, rat hot plate test, rat tail flick assay, and guinea pig toe pinch test). Interference with analgesia and opioid withdrawal symptoms were only seen at high doses of 30 mg/kg in mice.

- *Primary pharmacology*

The primary pharmacology of the compound was documented in one phase I urodynamic study performed by the applicant (Study MNTX 206), and a variety of studies performed at early stages of the development, which were only included as literature reports.

Study MNTX 206 tested the effect of naloxone and i.v. methylnaltrexone in reversing the opioid effects on bladder function in healthy volunteers. Naloxone successfully reversed opioid bladder effects, whereas administration of placebo had no effect on urinary retention. In contrast to placebo, MNTX reversed urinary retention in 27% of the subjects and had a clear albeit lower effect than naloxone on maximal detrusor pressure.

The evaluation of pupil diameter measurements revealed that MNTX exerted CNS effects similar to placebo, while the pure opioid-antagonist naloxone successfully reversed opioid-induced miosis. Thus, the absence of central effects of MNTX was concluded, while a partial antagonism to the (presumed peripheral) opioid effects on the urinary bladder could be seen.

Overall, MNTX did not exert CNS effects at notable levels while resulted able to (at least partially) reverse peripheral opioid effects. However, as the specific mechanism and receptor for the induction of the effects on the urinary bladder are not known, a clear conclusion regarding receptor specificity could not be drawn.

Literature studies revealed that MNTX at all dose levels and in all ways of administration (i.v., s.c. and oral) reverses the morphine-induced prolongation of oro-caecal transit time, which was considered a consistent proof of the  $\mu$ -receptor antagonising effect, as the pharmacology of morphine in the GI tract is well established.

Consistent results across the studies were also observed for the missing influence of MNTX on centrally mediated effects of opioids, including pain, and hypoxemia. Inconsistent results were observed for the reversal of opioid-induced subjective effects, such as nausea, vomiting, flushing, itching and others.

Early clinical studies concluded that MNTX is able to induce bowel movements in long-term users of opioids, but has, however, no consistent effect on post-operative nausea and vomiting.

- *Secondary pharmacology*

Cardiovascular safety – as part of the secondary pharmacology – was investigated because of adverse findings in animals regarding the prolongation of the QT interval. Furthermore, an early tolerance study (available as literature report only) resulted in a high rate of 37.5% cases of orthostatic hypotension in healthy volunteers when given and 0.64 mg/kg i.v. push-dose.

Despite a negative outcome of the *in vitro* studies on the isolated hERG-channel, a “thorough QT-study” according to the respective guideline (E 14; then available as concept paper recommendations) was performed due to findings in animals.

Study MNTX-1106 was conducted as a double-blind, placebo and positive controlled parallel group study, including a moxifloxacin arm as positive control. MNTX was investigated at 0.15 mg/kg (approx. the dose for routine clinical use), 0.30 mg/kg, and 0.50 mg/kg single s.c. doses. Moxifloxacin was given as a single 400 mg tablet (not blinded).

12-lead ECGs were performed at different time-points up to 24 hours on day 1 (baseline) and on day 1 (after dosing).

The primary ECG variables were QT/QTc interval duration (QTcI=individual corrected QT duration) measured from the 12-lead electronic ECG recordings. Secondary endpoints included the Bazett- and Fridericia-corrected QTc intervals. Additionally, a central tendency and outlier analysis (with standard categorical definitions) was performed.

A total of 546 healthy volunteers were screened for the study, of which 339 failed the screening criteria; thus, 207 subjects were enrolled (safety population), of which 206 successfully concluded the study. 7 subjects were excluded from the analysis due to inadequate ECG recordings. The five groups were comparable regarding the demographic characteristics. The subjects were 18-45 years old (inclusive), with a Body Mass Index (BMI) between 18-30 (inclusive), and weight between 50-110 kg.

The positive control produced a mean QTc prolongation that was significantly different from placebo and therefore consistent with published data, thus validating the sensitivity of the study.

Results showed that single s.c. doses of MNTX up to the suprathreshold dose of 0.50 mg/kg (approx. 3x the dose proposed for routine clinical use) did not produce any signal of an effect on QTc prolongation or any suggestion of an effect on secondary ECG parameters or waveform morphology. It was therefore concluded that the potential for QT prolongation from single s.c. doses of MNTX is expected to be – if any – very low.

#### *Relationship between plasma concentration and effect*

No analysis of the relationship of the plasma concentration and effect was performed out of the pharmacodynamic studies. An analysis with extrapolation of the estimated plasma levels in the clinical programme with the laxation responses observed was presented. No clear conclusions could be drawn by this rather unusual analysis, which was not based on pure pharmacodynamic investigations/endpoints, but on clinical response criteria and simulation of exposures. However, in view of the overall clinical results, no concern was derived from the missing of a proper PD/dose-response relationship analysis.

#### *Pharmacodynamic interactions with other medicinal products or substances*

The mechanism of action is competitive inhibition at  $\mu$ -receptors, and no further receptors were found to interact with the compound. For this reason, no additional studies on possible pharmacodynamic interactions were performed.

#### *Genetic differences in PD response*

Genetic differences in  $\mu$ -receptors or the whole opioid receptor system could not be regarded as being well-established. Therefore, no such investigations were performed.

### **Clinical efficacy**

The clinical program for the evaluation of efficacy of methylnaltrexone in the treatment of opioid induced constipation in palliative care patients with a life expectancy of 1 to 6 month included the studies described in the table below:

**Table 6:** Overview of the clinical programme.

Study ID	Design	Study Posology	Study Objective	Patients by arm entered/compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
MNTX 302	double blind, randomized, placebo-controlled	0.15mg/kg if necessary escalated to 0.30mg/kg or Placebo	onset of laxation	71 Placebo 62 MNTX 82 Extension	2 weeks double blind and 3 month open label	Male and female 70 years	opioid induced obstipation in palliative care patients	proportion of patients with laxation within 4 hours after administration
MNTX 301	double blind, randomized, placebo-controlled	fixed dose of 0.15mg/kg or 0.30mg/kg or Placebo	onset of laxation	52 Placebo 47/0.15 MNTX 55/0.30 MNTX	1 day double blind and 4 month open label	Male and female 66 years	opioid induced obstipation in palliative care patients	proportion of patients with laxation within 4 hours after administration
MNTX 251	double blind, randomized	fixed doses of 1, 5, 12.5, or 20mg	onset of laxation; dose ranging	33 MNTX	1 week double blind and 3 weeks open label	Male and female 61 years	opioid induced obstipation in palliative care patients	proportion of patients with laxation within 4 hours after administration

- **Dose response study (Study MNTX 251)**

This was a phase 2 dose ranging study with duration of up to 4 weeks. It was designed as a multi-centre, randomized, parallel group study with a double-blind period (week 1) and an open label period (weeks 2 through 4). Thirty-three patients were randomly assigned to receive fixed dose of MNTX (1, 5, 12.5, or 20mg QOD) under double blind conditions during the first week. Eighteen patients entered the open label period and were treated with doses between 5 and 20mg MNTX QOD for up to 3 weeks.

The study was conducted in patients with advanced medical illness and poorly controlled opioid induced constipation who were receiving palliative care. Additional inclusion criteria were the receipt of opioid medication for at least two weeks and a stable laxative regimen of any type for more than 4 days.

The primary efficacy endpoint was the laxation response on day one within four hours after study drug administration. Secondary efficacy endpoints included patient recorded evaluation of bowel movement, constipation, pain, opioid withdrawal effects and patient satisfaction.

The following table summarizes the proportions of patients who reported laxation within four hours, and then within 24 hours of dosing on day 1, 3, and 5 during the double blind phase.

**Table 7:** Laxation response within 24 hours (study MNTX 251)

Dosing Day	MNTX Dose Level					Chi-Square P-Value[1]
	1 mg	5 mg	12.5 mg	20 mg	≥5 mg combined	
<b>4-hour response</b>						
1	1/10 (10%)	3/7 (43%)	6/10 (60%)	2/6 (33%)	11/23 (48%)	0.1346
3	2/9 (22%)	4/6 (67%)	5/7 (71%)	2/4 (50%)	11/17 (65%)	0.1927
5	0/7 (0%)	4/5 (80%)	4/7 (57%)	3/4 (75%)	11/16 (69%)	0.0193
<b>24-hour response</b>						
1	5/10 (50%)	5/7 (71%)	7/10 (70%)	2/6 (33%)	14/23 (61%)	0.4136
3	3/9 (33%)	4/6 (67%)	5/7 (71%)	3/4 (75%)	12/17 (71%)	0.3316
5	1/7 (14%)	4/5 (80%)	4/7 (57%)	3/4 (75%)	11/16 (69%)	0.0903

Being the mean weight of the included patient population 65 kg, the doses applied in this study approximately correspond to 0.015mg/kg, 0.08mg/kg, 0.19mg/kg and 0.31mg/kg in the four groups.

The nominal p-values for individual comparisons for 4-hour laxation response on day 1 between the 1mg dose and the 5mg, 12.5mg, and 20mg doses were 0.05, 0.06, and 0.52, respectively. The lowest response rate was found in the 1mg group (10%). Clear and clinically relevant efficacy differences between the dose groups 5mg, 12.5mg and 20mg could not be observed. The choice of the 0.15mg and 0.30mg/kg doses had to be considered somewhat arbitrary, and was considered acceptable only because no dose-related safety signals were detected in the dose range investigated in the confirmatory trial.

- **Main studies**

#### **MNTX 301 / 301 EXT**

MNTX 301 was a multi-centre, phase 3 study that included a 1-day, double-blind, placebo-controlled period followed by a 4-week open label period. The study was conducted in patients with advanced medical illness and opioid induced constipation. The 301 EXT study was a 3-month open-label extension of the 301 study. Patients were randomized to receive a single dose of MNTX 0.15mg/kg (N=47), MNTX 0.30mg/kg (N=55), or Placebo (N=52). 136 patients participated in the 4-week open label period all treated with MNTX (0.05, 0.15, or 0.30mg/kg). 21 patients participated in the 3-month, open label extension study.

#### METHODS

##### *Study Participants*

Patients had to fulfil, among others, all of the following criteria to be eligible for entry into the 301 study:

- Advanced medical illness with a life expectancy of 1 to 6 month.
- No clinically significant laxation within 48 hours prior to the first dose of study drug
- On stable opioid regimen for the control of pain for three or more days before randomization. Stable was defined as no reduction in dose of 50% or more of the opioid dose within 3 days prior study drug administration.
- On a stable laxative regimen 3 or more days prior to treatment. The three day restriction on laxatives was applied to standing ordered laxatives. If a rescue laxative was given and was successful, an additional 48 hours without laxation had to elapse for the patient to be eligible to start the study.

Patients with any disease process suggestive of gastrointestinal obstruction or with any potential non-opioid cause of bowel dysfunction were not eligible.

### *Treatments*

In the double-blind period of the study patients were randomly assigned to receive one dose of methylnaltrexone (0.15mg/kg or 0.30mg/kg) or placebo in a 1:1:1 ratio. Study medication was administered subcutaneous in matching volumes. Patients who completed the single dose double blind period of the study (one single administration of the study drug) were eligible to enter the 4-week open label period and were to start treatment with a subcutaneous dose of methylnaltrexone 0.15mg/kg. Subsequent doses were adjusted (0.075mg/kg, 0.15mg/kg, or 0.30mg/kg) based upon efficacy or side effects. In the 301 EXT study, dosing was to begin with the dose level last received in protocol MNTX 301, and subsequent doses were adjusted to one of the three above mentioned dose levels at the discretion of the investigator.

The double blind medication was administered by a qualified study staff member. Subsequent doses were administered by a trained caregiver. Patients were to remain seated following dose administration.

### *Outcomes/endpoints*

The primary efficacy endpoint of the 301 study was laxation response within 4 hours of treatment. The patient (or caregiver) was asked to complete an assessment of each bowel movement using the ratings date and time of bowel movements, consistency of stool, and difficulties during defecation.

Secondary endpoints were the assessment of constipation distress, the assessment of pain, assessment of symptoms associated with opioid withdrawal, and the rating of the overall change in bowel status on a 7-point scale. Secondary endpoints were evaluated during both the double-blind and open-label periods. Additional secondary endpoints included:

- Laxation response within 24 hours of treatment;
- changes in a 5-point constipation distress scale
- changes in bowel movement consistency
- changes in bowel movement difficulty
- changes in pain scores
- changes in opioid withdrawal symptoms
- global clinical impression of change ratings
- use of rescue laxative medication
- changes in bowel movement frequency

No evaluation of quality of life parameters was included within the endpoints.

The 301 EXT study included also most of the above-mentioned efficacy endpoints, but clinical evaluations were only recorded monthly. This study provided mainly long-term safety data regarding methylnaltrexone administration.

### *Sample size*

The study was planned to accrue approximately 150 patients (50 per treatment arm). Comparison of each of the two doses of MNTX was made at the 0.025 Type I level of significance to adjust for multiplicity. 4-hour laxation responses recorded during a phase 2 study of methylnaltrexone in patients with advanced medical illness were on the order of 55% to 67% following doses of approximately 0.10-0.15mg/kg. Thus for this study a sample size of 50 patients per treatment group was determined to be able to detect a difference in the portion of responders on the order of at least 0.35.

### *Randomisation*

Patients were randomly assigned in blocks of three within each study centre to the three treatment groups in a 1:1:1 ratio according to a computer-generated randomization scheme.

### *Blinding (masking)*

A qualified designee at the study site assigned, recorded, and dispensed boxes of double-blind medication to the patients. Study drug (methylnaltrexone or placebo) was provided by the Sponsor in identical-appearing vials.

### *Statistical methods*

No per protocol analysis (for the primary endpoint of the double-blind study phase) were conducted because only 1 patient would have been ineligible. The efficacy analysis was to be performed on the intent-to-treat analysis set, which was defined as all randomized patients who received the double-blind dose of the study drug. Baseline values were to be the value recorded before administration of the double-blind dose of medication for the double-blind period of the study and the predose values measured before the first open-label dose.

The analysis of the primary endpoint was to be performed using the Cochran-Mantel-Haenszel test that included a comparison of methylnaltrexone against placebo and a term for treatment-by-centre interaction. If the interaction was statistically not significant, then a Chi-square test was to be used to compare each methylnaltrexone dose against placebo at the type 1 error level of 0.0249.

Among the secondary endpoints, the proportion of patients with a laxation response within 24 hours of treatment as well as the respective confidence intervals were calculated by randomized treatment group. The distributions of changes from baseline in the constipation distress scale and bowel movement assessments were summarized and compared between treatment groups. The proportion of patients with improvement in constipation distress and global clinical impressions of changes scores were summarized and compared between treatment groups.

Primary and secondary endpoints were explored to determine if any subgroup interactions were present. Factors to be included were age, gender, race, baseline constipation distress score, study site, primary disease, baseline opioids, and baseline WHO performance scale. Outcome variables were tabulated by treatment group and factor level. If any factor was significantly different between baseline treatment groups at or below the  $\alpha=0.10$  level, it may have been included in additional models to test the treatment-by-factor interaction in a multivariate model.

## Results

### *Participant flow*

A total of 154 patients were treated with a single double-blind dose, of which 147 patients entered the open-label period, 136 being treated with methylnaltrexone. 72 patients completed the open-label period and 75 patients discontinued prematurely. 27 patients entered the EXT study, 21 receiving at least one dose of methylnaltrexone.

Reasons for premature discontinuation are outlined in the following table.

**Table 8:** Reasons for discontinuation (study MNTX 301 and study MNTX 301 EXT).

Category	Total
Number of Patients Entering 301 OL Period	147 (100.0%)
Number of Patients Dosed in 301 OL Period	136 (92.5%)
Number of Patients Completed 301 OL Period	72 (49.0%)
Number of Patients Discontinued 301 OL Period	75 (51.0%)
Reason for Premature Discontinuation in 301 OL Period	
Ineligibility Determined	1 (0.7%)
Non-compliance	2 (1.4%)
Intolerable Adverse Event	4 (2.7%)
Withdrawal Request by Patient	7 (4.8%)
Disease Progression	8 (5.4%)
Adm. or Investigator Decision	2 (1.4%)
Lost to Follow-Up	1 (0.7%)
Death on Study	39 (26.5%)
Unresponsive to Treatment	5 (3.4%)
Other	6 (4.1%)
Category	Total
Number of Patients Entering 301 EXT Study	27 (100.0%)
Number of Patients Dosed in 301 EXT Study	21 (77.8%)
Number of Patients Completed 301 EXT Study	9 (33.3%)
Number of Patients Discontinued 301 EXT Study	18 (66.7%)
Reason for Premature Discontinuation in 301 EXT	
Noncompliance	1 (3.7%)
Withdrawal Request by Patient	4 (14.8%)
Disease Progression	1 (3.7%)
Death on Study	12 (44.4%)

### *Recruitment*

The first patient was enrolled in the study on the 11 February 2003. The last patient completed the study at the 28 February 2005.

### *Baseline data*

Baseline demographic characteristics in the three double-blind groups were comparable, as shown in the table below.

**Table 9:** Demographic and Baseline Characteristics for study MNTX 301; double-blind phase.

Characteristic <sup>a</sup>	Statistic/ Category	Placebo (N=52)	MNTX 0.15 mg/kg (N=47)	MNTX 0.30 mg/kg (N=55)	Total (N=154)
Age (years)	N	52	47	55	154
	Mean (SD)	64.7 (16.20)	65.9 (15.51)	65.3 (13.43)	65.3 (14.96)
	Median	62.5	67.0	68.0	66.0
	Min-Max	21-100	26-96	34-89	21-100
Sex, n (%)	Male	28 (53.8%)	25 (53.2%)	31 (56.4%)	84 (54.5%)
	Female	24 (46.2%)	22 (46.8%)	24 (43.6%)	70 (45.5%)
Race, n (%)	Caucasian	43 (82.7%)	38 (80.9%)	46 (83.6%)	127 (82.5%)
	Black	3 (5.8%)	5 (10.6%)	4 (7.3%)	12 (7.8%)
	Hispanic	5 (9.6%)	3 (6.4%)	4 (7.3%)	12 (7.8%)
	Asian	1 (1.9%)	1 (2.1%)	0	2 (1.3%)
	Other	0	0	1 (1.8%)	1 (0.6%)
Weight (kg)	N	51 <sup>b</sup>	47	55	153
	Mean (SD)	67.1 (19.12)	70.4 (21.08)	65.5 (16.03)	67.6 (18.71)
	Median	68.1	70.0	64.0	65.9
	Min-Max	29-133	31-135	31-110	29-135
Primary diagnosis, n (%)	Cancer	43 (82.7%)	37 (78.7%)	45 (81.8%)	125 (81.2%)
	Cardiovascular	2 (3.8%)	4 (8.5%)	2 (3.6%)	8 (5.2%)
	HIV/AIDS	0	1 (2.1%)	0	1 (0.6%)
	Other	7 (13.5%)	5 (10.6%)	8 (14.5%)	20 (13.0%)
WHO Performance Status <sup>c</sup> , n (%)	0	0	1 (2.1%)	0	1 (0.6%)
	1	2 (3.8%)	2 (4.3%)	1 (1.8%)	5 (3.2%)
	2	17 (32.7%)	13 (27.7%)	15 (27.3%)	45 (29.2%)
	3	21 (40.4%)	19 (40.4%)	30 (54.5%)	70 (45.5%)
	4	12 (23.1%)	12 (25.5%)	9 (16.4%)	33 (21.4%)
Oral morphine equivalents (mg/day)	N	52	47	55	154
	Mean (SD)	617.3 (1559.86)	3289.8 (17855.3)	1220.4 (4585.74)	1648.3 (10263.5)
	Median	150.0	207.0	188.0	186.5
	Min-Max	8-9720	10-122560	12-33120	8-122560

### *Outcomes and estimation*

#### Primary endpoint

Significantly more patients treated with either dose of MNTX had rescue free laxation **within 4 hours** of receiving the double blind dose of study drug compared with placebo-treated patients (see table below).

**Table 10:** Laxation response by treatment group after 4 hours: Double-blind patients (Study MNTX 301).

Time	Placebo (n=52)	0.15 mg/kg (n=47)	0.30 mg/kg (n=55)
<b>Number of Patients with Rescue-Free Laxation Response within the Time Interval</b>			
4 Hours	7 (13.5%)	29 (61.7%)	32 (58.2%)
95% Confidence Interval	4.2% - 22.7%	47.8% - 75.6%	45.1% - 71.2%
P-Value [1]		<0.0001	<0.0001
<b>Number of Patients with Laxation Response within the Time Interval (with or without Rescue)</b>			
4 Hours	7 (13.5%)	30 (63.8%)	32 (58.2%)
95% Confidence Interval	4.2% - 22.7%	50.1% - 77.6%	45.1% - 71.2%
P-Value [1]		<0.0001	<0.0001

[1] P-values are the nominal p-value in the pairwise comparison of each MNTX dose with placebo. Because of the interim analysis and comparison of each dose with placebo, p-values <0.0249 are considered statistically significant.

Laxation response 4-hours after dosing was 62% for the methylnaltrexone 0.15mg/kg group, 58% for the methylnaltrexone 0.30mg/kg group, and 13.5% for the placebo group. Thus, the superiority of MNTX over placebo in the induction of prompt laxation was clearly demonstrated.

#### Secondary endpoints

Significantly more patients treated with methylnaltrexone had rescue free laxation **within 24 hours** of receiving the double-blind dose of study drug compared with placebo-treated patients (see table below).

**Table 11:** Laxation response by treatment group after 24 hours: Double-blind patients (study MNTX 301).

Time	Placebo (n=52)	0.15 mg/kg (n=47)	0.30 mg/kg (n=55)
<b>Number of Patients with Rescue-Free Laxation Response within the Time Interval</b>			
24 Hours	14 (26.9%)	32 (68.1%)	35 (63.6%)
95% Confidence Interval	14.9% - 39.0%	54.8% - 81.4%	50.9% - 76.3%
P-Value [1]		<0.0001	0.0001
<b>Number of Patients with Laxation Response within the Time Interval (with or without Rescue)</b>			
24 Hours	17 (32.7%)	35 (74.5%)	35 (63.6%)
95% Confidence Interval	19.9% - 45.4%	62.0% - 86.9%	50.9% - 76.3%
P-Value [1]		<0.0001	0.0014

[1] P-values are the nominal p-value in the pairwise comparison of each MNTX dose with placebo. Because of the interim analysis and comparison of each dose with placebo, p-values <0.0249 are considered statistically significant.

Laxation response at 24 hours was 68% for the methylnaltrexone 0.15mg/kg group, 64% for the methylnaltrexone 0.30mg/kg group, and 27% for the placebo group, confirming the superiority of MNTX over placebo in the induction of laxation.

Results from the open label extension phase showed that comparable rates for laxation were found in all three (former) treatment groups, resembling the rates of the two groups with active treatment during the double-blind phase.

The time to laxation was significantly shorter for the active treatment groups compared to placebo in the double-blind treatment phase (1.10 hours and 0.8 hours versus >24 hours in the 0.15mg/kg, the 0.30mg/kg and the placebo groups respectively).

The comparison of bowel movement consistency and difficulty was hampered by the fact that only a few patients in the placebo group had bowel movements at all. As a result, the nominal figures showing similar results for improvement in all three treatment groups does not necessarily mean that stool consistency and difficulties with defecation remained at the same level in all three treatment groups. However, the study design (with the very short observation period) was considered inappropriate for the evaluation of this endpoint. Similar conclusions were drawn for the open-label phase of the study, because the number of patients remaining in the study decreased rapidly over time.

The evaluation of the subjective rating of constipation distress, however, resulted in a clear superiority of the two active treatment groups, with 63-64% of patients rating an improvement, as compared to 34% in the placebo group after 4 hours. Similar results were reported for the 24 hours evaluation.

The global clinical impression of change also revealed that a majority of patients (59%) felt better with active treatment, in comparison to only 22% in the placebo group.

### **Study MNTX 302**

Study MNTX 302 was a multi-centre phase 3, double-blind, randomized, placebo-controlled parallel group study in which patients were treated with 0.15 mg/kg MNTX s.c. (N=63) or placebo (N=71) every other day for 2 weeks. Dose escalation to 0.30 mg/kg was possible during the second week. The study was extended with a 3-month open-label extension phase (N=82) with dose adjustments to 0.075 or 0.30 mg/kg if necessary and administration was on an “as needed” basis with a maximum dosing frequency of 1 dose per 24 hours.

### METHODS

#### *Study Participants*

Among other inclusion criteria, patients had to have been taking opioid medication for the control of pain/discomfort for at least 2 weeks before the first dose of study drug with the regimen being stable for at least 3 days (“stable” being defined as “no reduction of  $\geq 50\%$ , increases being allowed). Opioid induced constipation was defined by either having less than 3 bowel movements during the previous week by history and without having a clinically significant laxation within the 24 hours before the first dose of the study drug, or without a clinically significant laxation within 48 hours prior to the first dose of the study drug (the latter definition was only introduced by protocol amendment 3 on 8<sup>th</sup> June, 2005, after already 111 patients had been included into the study).

Furthermore, patients had to be on a stable laxative regimen for at least 3 days before the first dose of the study drug (not counting rescue medication). In case of the use of a rescue laxative (including suppositories or enemas) an additional 24 hours (in case of less than 3 bowel movement during previous week) or 48 hours (in case of the 48 hours criterion) without laxation had to elapse for the patient to be eligible. Rescue laxative within 4 hours before the study drug dose were to be avoided.

Moreover, patients had to have advanced medical illness, however, with a predicted life expectancy of >1 month.

Exclusion criteria were, amongst others, the suspected potential of a non-opioid cause of bowel dysfunction, gastrointestinal obstruction, and faecal impaction.

### *Treatments*

Patients either received 0.15 mg/kg MNTX or placebo by s.c. injection. The first dose was administered by a staff member, and subsequent doses by a trained caregiver into the shoulder area, buttocks, abdomen, thighs, or extremities with rotation of injection sites.

The study drug was provided as vials each containing MNTX at a concentration of 40 mg/ml in 1.1 ml vehicle for single use (or identical placebo vials).

The starting dose was the same for all patients, given QOD for the first week. If a patient had less than 3 bowel movements by day 8 (not associated with rescue medication or intervention), the patient was then eligible to receive the double volume of the study drug (i.e. 0.30 mg/kg in case of MNTX) QOD.

### *Outcomes/endpoints*

Two co-primary endpoints were used in this study: the proportion of patients with laxation within 4 hours after the first dose of study drug and the proportion of patients with  $\geq 2$  laxations within 4 hours after dose administration over 4 doses (the first week of double-blind treatment).

Secondary endpoints were the following: the laxation responses within 4 hours of each dose of study medication, and the proportion of subjects with  $\geq 4$  laxations within 4 hours post dosing over 7 doses (the whole treatment period of 2 weeks).

Tertiary endpoints included the following: the proportion of patients with  $\geq 3$  laxations per week during double-blind dosing, the time to laxation onset post-dosing, the laxation responses within 24 hours following each dose, the number of laxations per week for each study week (week 1 and 2), the number of rescue-free laxations per week during double-blind dosing, the changes in bowel movement consistency, the changes in bowel movement difficulty, the changes in pain scores, the changes in opioid withdrawal symptoms (using a modified Himmelsbach scale), the global impression of change ratings by patients and assessors (GCIC), and the use of rescue laxative medication.

### *Sample size*

The sample size was estimated to be 130 patients (approx. 65 per patient group) with the following assumptions: a difference between the treatment and placebo group of 0.30 – 0.35 in either of the two primary endpoints and an assumed placebo response rate of 20% as well as an adjusted alpha level of 0.025 (two sided) and a power of 90%. The estimated differences were based on the response rates of study MNTX 251.

### *Randomisation*

Patients were randomly allocated to receive one of the two study drugs in a 1:1 ratio with block randomisation.

### *Blinding (masking)*

Same as for Study MNTX 301.

### *Statistical methods*

The co-primary analyses were to be performed on the ITT analysis set by Cochran-Mantel-Haenszel test of placebo against MNTX with study centre as stratification factor. If there was no significant treatment-by-centre interaction observed (with a p-value of  $\leq 0.10$ ) the primary endpoint was to be analysed with a Chi-square test. Response rates will be calculated and presented with 95% confidence intervals.

For the one- and two weeks evaluations the LOCF method was to be used.

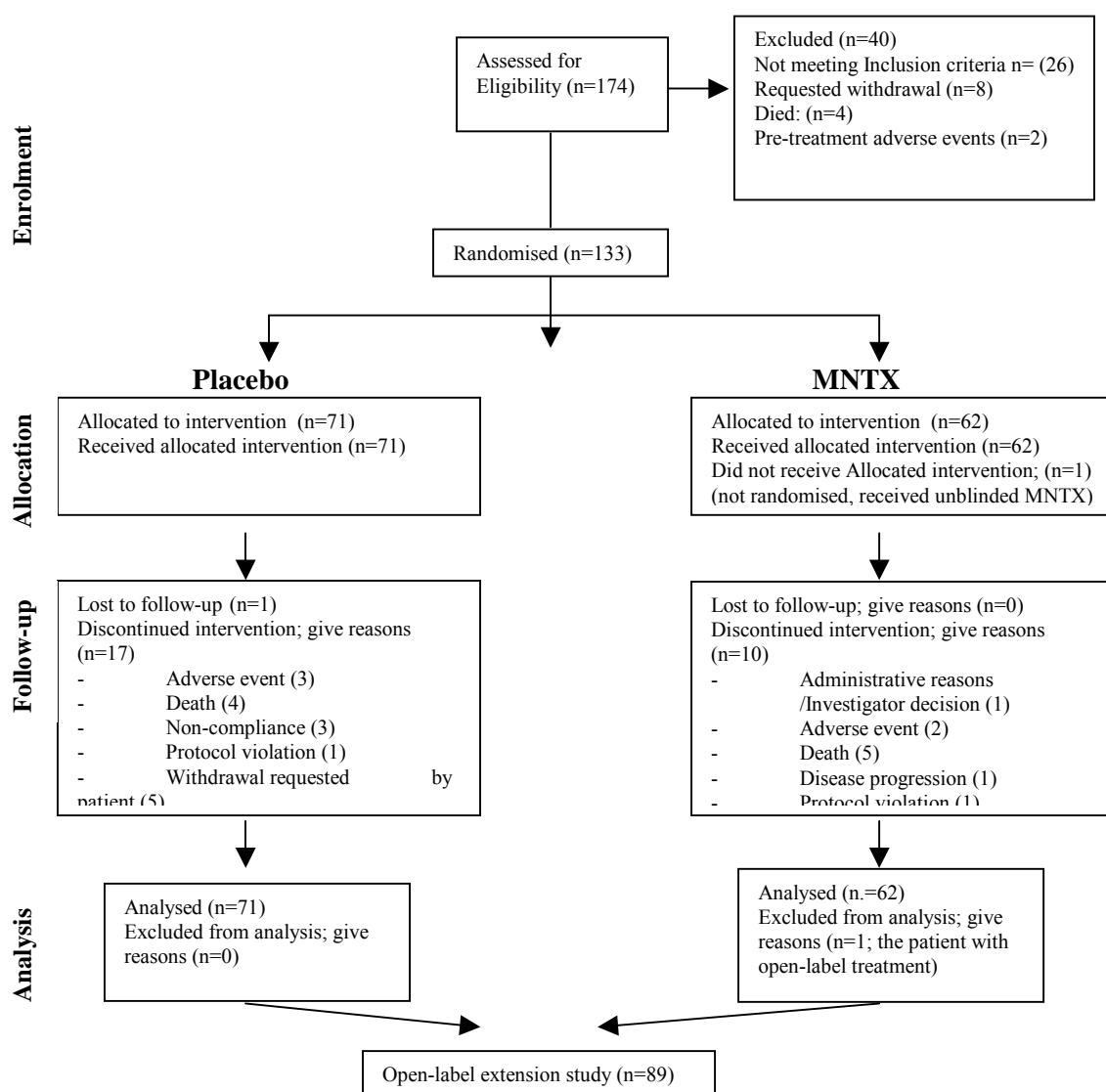
The analysis of the secondary endpoints was to compare placebo to all possible MNTX doses combined, as well as to the doses received.

The nominal type I error of significance for secondary and tertiary endpoints was 0.05. For the primary endpoints this level was adjusted to 0.249 to account for multiple comparisons and the interim analysis performed (see below).

An interim analysis was planned after approx. 50% of the patients had completed the double-blind period in order to assess safety of MNTX and to re-estimate the sample size, thus ensuring that enough subjects were enrolled to preserve adequate power. An alpha level adjustment of 0.000076 was made to preserve the alpha level of 0.0249 for the final analysis. Safety data were analysed by the DSMB (consisting of 2 clinicians and 1 biostatistician). The efficacy results were analysed by a biostatistician who was external to both the DSMB and the sponsor and the results were presented to the DSMB, which recommended that the sponsor continue the study as planned with no change in sample size. According to the study report, the sponsor did not receive copy of the interim analysis.

## RESULTS

### Participant flow



### Recruitment

The study was conducted in 26 centres, located in Canada and the US. The study began on 28<sup>th</sup> February 2004 and ended on 16<sup>th</sup> October 2005. As is known from the protocol amendment No. 3, (8<sup>th</sup> June 2005), during the first 15 months of the study, 111 patients were recruited and randomized, and accordingly 24 patients after the protocol amendment. (approx. 4 months). Recruitment was therefore rather slow, with 7.4 patients/month before the protocol amendment, and 6.0 patients/month after the amendment.

### Baseline data

In the vast majority of characteristics clinically relevant differences were not seen. The majority of patients were Caucasian and cancer patients. A higher percent of patients in the MNTX group

(14.3%) had COPD and/or emphysema than in the placebo group (7.0%). All other disease-related characteristics appear to be relatively well balanced with the exception of the opioid dose/day, which was considerably higher in the MNTX group (417.0 mg) than in the placebo group (339 mg).

#### Numbers analysed

The efficacy analyses were performed in the ITT analysis set, which included all randomised patients who received at least 1 dose of study drug (71 placebo, and 62 MNTX).

The one patient excluded from the ITT set was an 88-year old female who was incorrectly entered into the study without being randomised, and was given unblinded MNTX from a supply of open-label medication intended for the extension phase of the study. The patient is therefore only included in the safety analysis.

No per-protocol evaluation was performed, as no exclusion for major protocol violations had to be performed.

#### Outcomes and estimation

##### Primary and secondary endpoints

The two primary efficacy endpoints showed highly significant results in comparison to placebo (see table below).

**Table 12:** Summary of results of primary efficacy endpoints (ITT; LOCF)

	Placebo (71)			MNTX (62)			p-value <sup>a</sup>
	Patients Dosed	Patients with Laxation Response	Percentage of Responders (95% CI)	Patients Dosed	Patients with Laxation Response	Percentage of Responders (95% CI)	
Laxation within 4 hours on Day 1	71	11	15.5 (7.1 - 23.9)	62	30	48.4 (35.9 - 60.8)	p<0.0001
At least 2 laxations within 4 hours over the first 4 doses	71	6	8.5 (2.0 - 14.9)	62	32	51.6 (39.2 - 64.1)	p<0.0001

The laxation responses after the single doses are given in the table below.

**Table 13:** Laxation response (rescue free) within 4 hours after each dose (analysis set: ITT).

	Placebo (N=71)			MNTX (N=62)		
	Patients Dosed	Patients with Laxation Response (%)	95% Confidence Interval (CI)	Patients Dosed	Patients with Laxation Response (%)	95% Confidence Interval (CI)
Dose 1 (Day 1)	71	11 (15.5)	7.1-23.9	62	30 (48.4)	35.9-60.8
Dose 2 (Day 3)	65	6 (9.2)	2.2-16.3	57	26 (45.6)	32.7-58.5
Dose 3 (Day 5)	63	8 (12.7)	4.5-20.9	58	27 (46.6)	33.7-59.4
Dose 4 (Day 7)	59	4 (6.8)	0.4-13.2	56	21 (37.5)	24.8-50.2
Dose 5 (Day 9)	58	8 (13.8)	4.9-22.7	56	23 (41.1)	28.2-54.0
Dose 6 (Day 11)	52	5 (9.6)	1.6-17.6	51	19 (37.3)	24.0-50.5
Dose 7 (Day 13)	51	4 (7.8)	0.5-15.2	47	18 (38.3)	24.4-52.2
Overall Response	71	33 (46.5)	34.9-58.1	62	49 (79.0)	68.9-89.2

Similar results were seen in the evaluation of all doses for the 24 hours time-point, although with somewhat higher rates in both the placebo and MNTX groups, but with similar differences.

The secondary endpoints were generally in support of the primary endpoints. The laxation response over all 7 doses was 5.6% in the placebo group and 38.7% in the MNTX group. The number of patients with a dose adjustment in the second week was equal between the treatment groups (about 30% each). The time-related evaluations (time to laxation within 4 and 48 hours of dose 1) also showed a significant superiority of MNTX over placebo.

Evaluation of the laxation responses per week and of the “constipation criterion” regarding frequency (patients with at least 2 laxations per week) revealed that a significantly higher proportion of MNTX-treated patients achieved a “satisfactory” weekly bowel movement frequency. However, the overall frequency of bowel movements during the second week was not different between the treatment groups, possibly indicating a similar efficacy of MNTX treatment with standard and rescue laxative treatment combined.

Patients that had a dose escalation during the second week of treatment had a moderate increase in response rates in the MNTX group (from 15% to 24%) but not in the placebo group (from 8% to 7%).

Evaluation of stool consistency could only be assessed in patients who actually had bowel movements. Patients with watery bowel movements were equally distributed between the treatment groups (16.7% in the placebo group and 15.9% in the MNTX group).

Evaluation of the rating of bowel movement difficulties revealed a clear and stronger improvement in the MNTX groups in comparison to placebo. Likewise, evaluation of constipation distress revealed overall better results for MNTX as compared to placebo, however, with diminishing superiority towards the end of the observation period.

Also, the global impression of change as assessed by the patients and the treating physicians revealed a clear superiority of MNTX over placebo for the first, as well as for the second week of treatment.

An additional, explorative evaluation of response rates incorporating the criteria bowel movement frequency (at least 3 per week), stool consistency and defecation symptoms according to severity at baseline was performed. This evaluation revealed that a significant treatment effect could be preserved even if these criteria for “functional obstipation” patients were applied. However, the therapeutic effect was greatest in those most severely affected but was diminished in those with only mild or no such symptoms. In particular, when looking at the more objective criterion of “stool consistency rating”, there was no relevant difference between MNTX and placebo (38.5% versus 35.5% respectively).

### ***Ancillary analyses***

#### **- Opioid withdrawal**

The changes in pain scores over time (up to 14 days) were evaluated in the two pivotal studies to prove that MNTX does not exert central effects. No differences were seen between the treatment groups, indicating no consistent effect of MNTX on analgesia. Likewise, the evaluation of the withdrawal symptoms according to the 7 items “Modified Himmelsbach Withdrawal Scale” (rhinorrhea, tremor, piloerection, yawning, restlessness, perspiration, and lacrimation) did not reveal consistent differences between the treatment groups, indicating that MNTX is not causing clinically relevant opioid withdrawal symptoms.

#### **- Laxative use**

The evaluation of laxatives use in the two pivotal studies did not reveal differences between treatment groups. Almost all of the patients used laxatives at inclusion and the use of laxatives increased to 100% during the course of the study, in both treatment groups. Interestingly, the use of enemas increased relative to baseline from 14 to 35% in the placebo, and from 12 to 24% in the MNTX group respectively. It is also interesting to note that a general shift in the type of laxatives was observed during the study to the increased use of osmotic agents in the placebo group (from 33.8% to 40.8%) in comparison to MNTX (30.2% to 33.3%).

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

Given the described differences between the studies, the applicant was not able to perform a complete meta-analysis of the submitted data. However, the results for the primary endpoint (“% of patients with laxation within 4 hours after administration of first double-blind dose of study drug”) were

pooled for the two main studies (MNTX 301 and MNTX 302), and this analysis was also used to exclude any relevant effect of age or gender on overall efficacy, as shown in the following table.

**Table 14:** Number (%) of patients with laxation within 4 hours after administration of first double-blind dose of study drug (studies MNTX 302, 301) – by age and sex.

	Placebo (N=123) n (%)	MNTX (N=165) n (%)
Age < 65 years	9/61 ( 14.8)	38/66 ( 57.6)
Age ≥ 65 years	9/62 ( 14.5)	53/99 ( 53.5)
Female	12/64 ( 18.8)	48/82 ( 58.5)
Male	6/59 ( 10.2)	43/83 ( 51.8)

Additionally, these results were also analyzed using logistic regressions with sex, age, and baseline opioid use as covariates, as shown in the following table:

**Table 15:** Number (%) of patients with rescue –free laxation within 4 hours after first double-blind dose of study drug – logistic regression with sex, age and baseline opioid use as covariates (pooled results of MNTX 301 and MNTX 302).

	Placebo (N=123)	MNTX (N=165)	Parameter Estimate	p-Value
Number (%) of patients with response	18 ( 14.6)	91 ( 55.2)		
Logistic regression with sex as covariate				
Treatment group (MNTX or placebo)			0.9972	<0.0001
Sex			0.1938	0.1497
Logistic regression with age as covariate				
Treatment group (MNTX or placebo)			0.9917	<0.0001
Age <65 vs. Age ≥65			0.0614	0.6506
Logistic regression with baseline opioid dose as covariate				
Treatment group (MNTX or placebo)			1.0014	<0.0001
Baseline opioid dose			-0.00005	0.3697

From this evaluation, it was concluded that age and gender did not have influence on the response rates.

- **Clinical studies in special populations**

No such studies were performed. The target patient population is a special patient population in itself.

- **Supportive study(ies)**

One supportive study was conducted as an open-label 3-month extension of study MNTX 302, performed to obtain long-term safety and efficacy data.

Enrolment into the study had to be performed within 28 days of the completion of MNTX 302.

All patients had to begin treatment with the dose of 0.15 mg/kg. Dosing was to be performed on an “as needed” basis for up to 3 months. The investigators were permitted to increase the dose to 0.30 mg/kg, or to decrease it to 0.075 mg/kg at any time in order to achieve the desired clinical effect, or to ameliorate adverse effects. The highest permitted dose therefore was defined as 0.30 mg/kg per day.

Efficacy was assessed by bowel movement response (laxation response) as well as by the patients’ evaluations of consistency, and difficulty of bowel movements and constipation distress, together with the global ratings of patients and investigators. Withdrawal symptoms and assessment of pain were also recorded. All these parameters were recorded with the same methods as in study MNTX 302.

The following parameters were assessed on a daily basis: Bowel movement (including consistency and difficulty), concomitant medication and adverse events. Other parameters of efficacy and safety were only evaluated on a monthly basis: Global clinical impression of change (GCIC), pain evaluation, modified Himmelsbach scale, evaluation of constipation, adverse events, and concomitant medication.

Laxation responses were evaluated as patient response rate (number of doses with laxation response divided by total number of doses taken) and as dose response rate (number of doses with laxations response divided by total number of doses taken for all patients combined).

Other efficacy evaluations included the time to laxation onset, changes in stool consistency and in bowel movement difficulty, changes in pain scores and opioid withdrawal symptoms, the GCIC ratings, and the use of rescue laxative medication.

Of the 107 patients that completed protocol MNTX 302, 82 were included in the extension phase. Of these, only 32 completed the whole 3 months treatment period.

The highest numbers of discontinuation occurred due to death on study, a finding that was not unexpected considering the included patient population.

Among those patients that requested withdrawal themselves, 2 withdrew before receiving the first dose, and 9 (=approx. 10%) (4 from the former placebo group and 5 from the former MNTX group) withdrew due to unresponsiveness.

The two subsets of patients were quite similar regarding baseline characteristics and did not differ to a clinically relevant level as compared to the groups included in the double-blind phase of the study.

Overall, patients in the extension who continued to receive MNTX maintained the responses they had attained during double-blind treatment, and those patients who switched from double-blind placebo to open-label MNTX attained and maintained responses similar to those produced by double-blind MNTX.

The median time to rescue-free laxation response remained fairly constant over time with 0.60 hours at the beginning of the study and fluctuating between 0.42 and 0.73 hours.

The assessment of stool consistency was again only assessed with uninformative tables of shifts, however, with the figure of watery stools remaining at a fairly low level of 11%.

The overall rate of “moderate, considerable or great” difficulties after any of the 736 doses that led to a rescue-free laxation within 4 hours was given with 33.0%, which is identical to the rate in the MNTX group in the double-blind phase of the study, and lower than the rate for placebo (50%).

Constipation distress was also again evaluated by tables of shifts that were likewise not easy to interpret. The number of patients with absence of constipation distress were 45% on day 1 (4 hours after administration of the first dose), 27% after 4 weeks of treatment, with 18% after 8 weeks, and 18% after 12 weeks.

The use of laxatives during the course of the study was again monitored, with contact laxatives (89%), softeners, emollients (48%), and osmotically acting laxatives (38%) being the most commonly used drug classes. The frequency of enema use was still 31.7%.

There was overall little change in the pain scores throughout the course of the open-label extension. Likewise, there were no meaningful changes in mean or median values or in the range of changes of the total or single items of the Himmelsbach score for the measurement of withdrawal symptoms. Less than 5% of patients shifted from “none” or “mild” at baseline to “moderate” and no patients shifted to a severe rating for yawning and lacrimation. On the other hand, maximally 2 patients had such a shift for the other five items of the scale.

In conclusions, the results of the double-blind phase of the study were confirmed, and it was shown that efficacy could be maintained over a three-month period of time without causing an increase in pain scores or withdrawal symptoms.

#### • **Discussion on clinical efficacy**

The clinical studies performed – 1 phase 2 and 2 phase 3 studies – proved that MNTX is reliably able to induce a relatively prompt laxation in patients that are already treated with laxatives for opioid induced constipation and have ongoing difficulties with defecation.

The patients included were receiving palliative opioid therapy for various advanced illnesses, the majority being cancer. Most of the patients had a WHO performance status of 3 or 4. However, the

population investigated was rather small, and the duration of the double-blind phases of the performed studies was limited.

There was furthermore some indication that the compound relieves defecation complaints and improves stool consistency over the short term, leading to an overall patient satisfaction that is clearly distinct from placebo.

Open label extension studies showed that the a.m. effects can be maintained up to three months.

Among the concerns that were identified during assessment from the overall clinical development programme, the following are of note:

- The primary efficacy criteria used in the main clinical studies appeared to investigate the use of the drug as a rescue medication on top of the current “standard of care”, rather than the continuous treatment of constipation aiming at normalisation of bowel movement frequency, stool consistency and defecation complaints. Therefore, the intended indication “opioid induced constipation” was put under question and it was suggested to replace it with an expression more adequately reflecting the “emergency”-type use of the drug (e.g. “Induction of laxation in patients with opioid bowel dysfunction with inappropriate treatment response to conventional laxatives and with advanced illness”). In order to elucidate whether a regular “treatment of obstipation” could be achieved by the compound, the applicant was requested to perform a re-analysis of “responders” according to the following criteria:
  - normal bowel movement frequency (e.g. no constipation = at least 3 bowel movements per week)
  - normal stool consistency (assessment of stool as 2, 3, or 4 on the scale used)
  - no relevant defecation symptoms (“difficulty to pass stool” ratings 1 and 2 on the scale used)

This explorative analysis was also to be presented comparing the more severely affected population with the less severely affected patients.

The re-analyses resulted in the following:

**Table 16:** Re-analysis of MNTX 302 data utilizing a composite endpoint incorporating bowel movement frequency, stool consistency, and defecation symptoms according to baseline severity.

MNTX 302 Population	Proportion of responders		p-Value (Chi-square test)
	Placebo	MNTX	
ITT (n = 133)	19.7%	41.9%	0.0053
ITT for subjects admitted solely under criterion of no bowel movement for 48 hours (more than 3 bowel movements/week at baseline; n = 8)	42.9%	100%	0.2850
ITT for subjects admitted solely under criterion of no bowel movement for 48 hours (n = 125)	17.2%	41.0%	0.0033
ITT only with baseline Constipation Distress of “none” or “little bit” (n = 27)	42.9%	23.1%	0.2760
ITT only with baseline Constipation Distress of “somewhat”, “quite a bit” or “very much” (n = 103)	14.3%	46.8%	0.0003
ITT only with baseline Bowel Movement Difficulty of no, slight, or moderate (n = 59)	29.0%	39.3%	0.4061
ITT only with baseline Bowel Movement Difficulty of considerable, or great (n = 72)	12.5%	46.9%	0.0012
ITT only with baseline Stool Consistency Rating of soft, firm, or slightly hard (n = 57)	35.5%	38.5%	0.8164
ITT only with baseline Stool Consistency Rating of hard, or very hard (n = 65)	8.8%	51.6%	0.0002

Abbreviation: ITT=intent-to-treat  
 Responder defined as:  $\geq 3$  bowel movements/week with majority ( $\geq 50\%$ ) of stools reported as soft to slightly hard, and no or slight defecation difficulty

These analyses were considered overall reassuring in that the more severe the constipation symptoms appeared to be, the higher response could be expected from the treatment with MNTX. However, the

re-analysis did not lead to a similar reassurance for patients with mild constipation at baseline. This has been reflected in the SPC (section 5.1), which specifies that “stool consistency was not meaningfully improved in patients who had soft stools at baseline”.

- Most of the patients were included on the sole criterion of “delayed” defecation of more than 48 hours, without a clear definition of the three items that define the term constipation; i.e. reduced frequency, increased consistency and difficulties with defecation.

However, the vast majority of patients in the pivotal trials did report less than 3 bowel movements for the week prior to randomization, clearly demonstrating that these patients had decreased bowel movement frequency. Moreover, most reported substantial constipation distress, and a high degree of defecation difficulty, and many reported hard stool consistencies at baseline as well, suggesting that they adequately represent a population with substantial constipation severity, which is the intended patient population. Overall, all patients in the pivotal trials were terminally ill, were on high dose of opioids, and were identified by their clinicians as having opioid induced constipation. Despite a bowel regimen with a median of two laxatives, these patients had not had a bowel movement in at least 48 hours. Moreover, the overall life expectancy of the patients enrolled in the studies was consistent with a judgement of a median survival less than 6 months. As a result, it was agreed to restrict the indication to patients with limited life expectancy in palliative care.

- Results from the dose finding study MNTX 251 led to concerns over the 0.15 mg/kg and 0.30 mg/kg doses chosen for the main efficacy studies, as these doses initially appeared to be inappropriate to find the lowest effective dose in clinical practice. The applicant presented dose-response profiles suggesting that the 0.15 mg/kg dose (or not much lower) is likely to be the lowest dose at which the maximum response rate for s.c. MNTX could still be attained. Also, from the 90% confidence limit it appeared that, as expected based on the sample size, the response rates obtained with doses of 0.02, 0.08, 0.2 and 0.33 mg/kg carried considerably greater uncertainty than those with placebo, and doses of 0.15 mg/kg and 0.3 mg/kg. Overall, the 0.15 mg/kg dose seemed to provide an acceptable balance between efficacy and GI tolerability.

- The recommended dose of methylnaltrexone bromide reported in the SPC is 8 mg (0.4mL) for patients weighing 38-61 kg or 12 mg (0.6mL) for patients weighing 62-114 kg. The fixed dose regimen with the two strengths proposed by the applicant for the chosen weight bands was considered appropriate. The notion of fixed dose is in fact highly preferable both for ease of use and for decreasing the risk of administering the wrong dose. However, it remained unclear whether the proposal of treatment weight-related dosing of 0.15 mg/kg for subjects above or below these weight bands was still appropriate. Ultimately, no safety concerns were identified for patients weighing less than 38 kgs (for whom there is a risk on under-dosing), whereas the risk of overdosing for patients above 114 kgs was associated with (dose-related) higher risk of abdominal pain and dizziness, which were however mild adverse events. Thus, it was demonstrated that the treatment proposal for patients outside the chosen weight bands was acceptable.

In order to permit the proper assessment of the doses administered in both efficacy studies, the applicant was asked to present results of subgroups receiving oral, transdermal and intratechal therapy as well as the characterisation and results of the different subgroups receiving different substances or groups of substances (with potentially differential potential for obstipation, e.g. methadone or fentanyl, or with differences of binding capacity to the receptor). An overview on the further course of opioid intake during the course of Study MNTX 302 and its extension phases, together with their possible impact on response rates, was also requested. The applicant responded that it was not possible to analyse the data by subgrouping into patients receiving oral, transdermal or intratechal opioids, as there were only few patients receiving transdermal or intratechal opioids without receiving also oral opioids. It was therefore agreed that the number of patients was too low to allow for an analysis by subgrouping. Ultimately, it was demonstrated that MNTX efficacy was significantly superior to placebo regardless of the opioid dose employed.

### **Clinical safety**

The safety of methylnaltrexone was investigated in six phase 1 studies, one phase 2 study and two phase 3 studies with open label extensions. Subcutaneous methylnaltrexone was investigated in studies MNTX 103, MNTX 1105, MNTX 1106, MNTX 1107, MNTX 251, MNTX 301, and MNTX

302. All of these studies were complete at the time of the data cut off (1 September 2006), when there was one other ongoing, open-label, compassionate use study with s.c. methylnaltrexone.

- **Patient exposure**

**Table 17:** Patient exposure (cut-off date, 1 September 2006)

	Study number	Subjects /Patients enrolled	Subjects/Patients exposed	Patients exposed to the proposed dose range	Patients with long term safety data
Pharmacokinetic	MNXT 103	6	6		
Pharmacokinetic	MNTX 1105	32	32		
Pharmacokinetic	MNTX 1107	24	24		
Pharmacokinetic/ Placebo controlled	MNTX 1106	207	163	79	
Dose ranging	MNTX 251	33	33	20	
Placebo controlled	MNTX 301/301EXT	154	150	150	21
	Study number	Subjects /Patients enrolled	Subjects/Patients exposed	Patients exposed to the proposed dose range	Patients with long term safety data
Placebo controlled	MNXT 302/302EXT	134	134	134	82
Compassionate use	MNTX 901	24	24		

Long term safety data referring to treatments longer than 3 month are not available. Safety data referring to the maximally proposed dosing of 1 dose/day are also not available. In studies MNTX 301/301 EXT and MNTX 302 EXT the dosing interval between two administrations of methylnaltrexone was 3.6 day and 6.0 days respectively, with a range of 1 to 14 days in study MNTX 301/301 EXT and 2 to 40 days in study MNTX 302 EXT. Likewise the placebo-controlled phases of these studies only investigated a single-dose or a QOD dosing (for two weeks).

- **Adverse events**

Adverse events were counted as treatment-emergent for the placebo controlled and double blind pools if they occurred 1) at any time between administration of the first dose of study drug and the start of open label methylnaltrexone treatment for patients who received open label treatment, or 2) at any time between administration of the first dose of study drug and 30 days after the last dose of study drug for patients who received only double blind treatment. Adverse events were counted as treatment-emergent for the methylnaltrexone exposure pool if they occurred at any time between administration of the first dose and the last dose of methylnaltrexone.

In the methylnaltrexone overall pool, treatment emergent adverse events occurred in 97.9% of the patients who received at least one dose of methylnaltrexone. The incidence of adverse events was highest within the system organ class 'Gastrointestinal disorders' (73.8%) and 'General disorders and administration site conditions' (54.5%). The most frequent events were abdominal pain (39.2%), nausea (22.4%), vomiting (18.5%), flatulence (17.8%), diarrhoea 12.8%, pain (15.4%), peripheral oedema (14.3%), malignant neoplasm progression (31.8%), anxiety (15%), confusional state (12.6%), restlessness 11.2%, dyspnoea 12.2%, and hyperhidrosis (13.3%).

In the placebo-controlled pool treatment emergent adverse events occurred in 67.5% of the patients who received placebo and 80.6% of the patients who received methylnaltrexone in the placebo

controlled double blind studies. The table below shows the rate of adverse events within the different organ classes.

**Table 18:** Rates of adverse events according to System Organ Class.

Primary System Organ Class	Double-Blind Treatment	
	Placebo (N=123) n (%)	MNTX (N=165) n (%)
Any Primary System Organ Class	83 (67.5)	133 (80.6)
Gastrointestinal Disorders	43 (35.0)	87 (52.7)
General Disorders and Administration Site Conditions	36 (29.3)	48 (29.1)
Nervous System Disorders	19 (15.4)	37 (22.4)
Psychiatric Disorders	25 (20.3)	35 (21.2)
Respiratory, Thoracic and Mediastinal Disorders	22 (17.9)	32 (19.4)
Investigations	14 (11.4)	25 (15.2)
Skin and Subcutaneous Tissue Disorders	16 (13.0)	20 (12.1)
Musculoskeletal and Connective Tissue Disorders	11 (8.9)	17 (10.3)
Infections and Infestations	11 (8.9)	14 (8.5)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	17 (13.8)	13 (7.9)
Injury, Poisoning and Procedural Complications	14 (11.4)	9 (5.5)
Metabolism and Nutrition Disorders	13 (10.6)	8 (4.8)
Cardiac Disorders	10 (8.1)	7 (4.2)
Vascular Disorders	10 (8.1)	6 (3.6)
Eye Disorders	1 (0.8)	4 (2.4)
Renal and Urinary Disorders	6 (4.9)	2 (1.2)
Blood and Lymphatic System Disorders	2 (1.6)	2 (1.2)
Ear and Labyrinth Disorders	0	2 (1.2)
Social Circumstances	0	2 (1.2)
Reproductive System and Breast Disorders	0	1 (0.6)
Hepatobiliary Disorders	2 (1.6)	0

Abbreviation: MNTX = methylnaltrexone.

Data on adverse events from the double blind treatment studies are limited. The rate of adverse events within the system organ classes ‘Gastrointestinal disorders’ and ‘Nervous system disorders’ was higher in the methylnaltrexone group than in the placebo group. Specifically, abdominal pain occurred in 28.5% of patients treated with methylnaltrexone but only in 9.8% of patients treated with placebo. The same trend could be observed for flatulence (13.3% versus 5.7%), diarrhoea (5.5% versus 2.4%) and nausea (11.5% versus 4.9%). The rate for dizziness was 7.3% in the methylnaltrexone group and 2.4% in the placebo group. For all other adverse events the event rates were comparable in both groups. The severity of adverse events was comparable in the methylnaltrexone and the placebo group. The incidence of adverse events was in general not different in the two active treatment groups (methylnaltrexone 0.15mg/kg and 0.30mg/kg). However, abdominal pain occurred in 38.2% of the patients in the 0.30mg/kg dose group and in 23.6% of the patients in the 0.15mg/kg dose group. As described in the efficacy section, data from patients treated with lower doses of methylnaltrexone were not available for the placebo controlled population.

- **Serious adverse event/deaths/other significant events**

At least 1 fatal serious adverse event occurred in 11 (8.9%) of the placebo-treated patients and in 2 (1.2%) of the methylnaltrexone-treated patients in the placebo controlled pool, and in 11 (8.9%) of the placebo-treated patients and in 5 (2.5%) of the methylnaltrexone-treated patients in the double blind pool.

Within the methylnaltrexone exposure pool, serious adverse events occurred in 57 (19.9%) of the 286 treated patients. The most commonly reported events were nausea, vomiting and chest pain, each occurring in 4 (1.4%) patients. None of the subjects in the healthy volunteers pool had a serious adverse event.

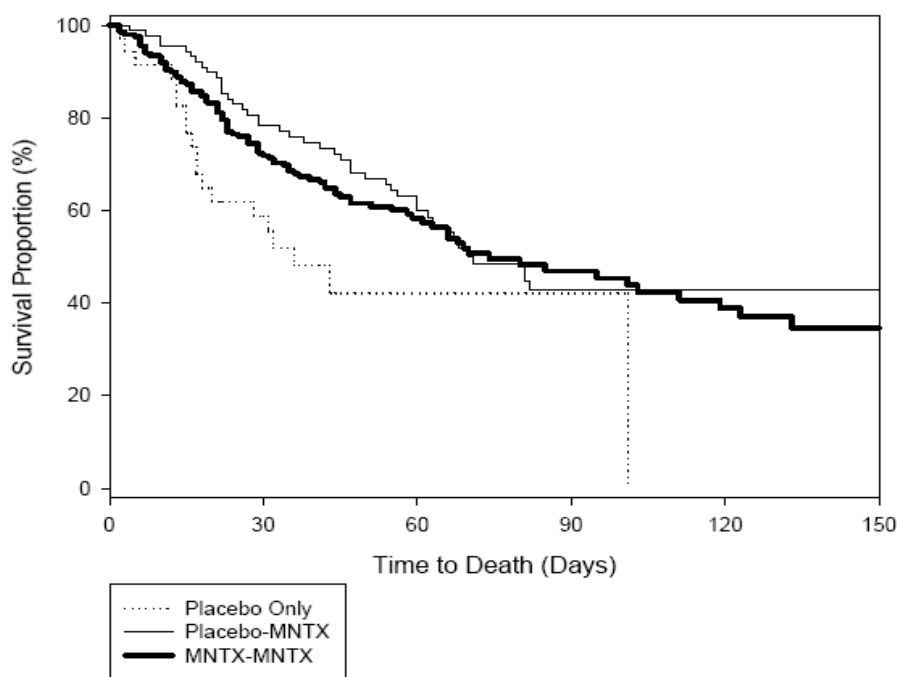
The frequency of serious adverse events was relatively low with regard to the special study population with a life expectancy lower than 6 month. Higher incidences in comparison to placebo-treated patients could not be observed in the double blind treatment pool.

No subject in a phase 1 study died. In the placebo controlled pool, 18 (14.6%) of the 123 placebo-treated patients and 16 (9.7%) of the 165 methylnaltrexone-treated patients died during or after the study. In the double blind pool, 18 (14.6%) of the 123 placebo-treated patients and 23 (11.6%) of the 198 methylnaltrexone-treated patients died during or after the study. The death reported for these

populations either occurred during the double blind treatment or were reported at the 30-day follow up contact for a patient who did not enter an open label study.

Of the 286 patients in the methylnaltrexone exposure pool, 140 (49.0%) died. The median survival was estimated at 70 days. The Kaplan-Meier survival curve based on combined double blind and open label treatment for all patients in the phase 2 and phase 3 studies is presented below (Figure 2). The survival of patients who received methylnaltrexone was no worse than that of patients who received placebo.

**Figure 2:** Kaplan-Meier survival curve by double-blind/open label treatment.



Death was the most frequently reported reason for premature discontinuation. A higher incidence of death due to the administration of methylnaltrexone could not be observed.

- **Laboratory findings**

The incidence of adverse events related to abnormal laboratory test results was low in both the placebo and the methylnaltrexone treated patients. This applies for the double blind and also for the open label studies as well as for study MNTX 203 (intravenous administration).

- **Safety in special populations**

#### **Renal impairment**

Study MNTX 1105 enrolled subjects with renal impairment. Two of eight subjects with mild renal impairment had adverse events (fatigue and paresthesia). One of eight subjects with moderate renal impairment had adverse events (diarrhoea, dyspepsia, and injection site stinging). One of 8 subjects with severe renal impairment had adverse events (dyspepsia, headache, hot flush, and vomiting). The events were all mild to moderate in intensity. For the double blind pool and the methylnaltrexone exposure pool of the controlled clinical studies there was no consistent pattern of increasing rates of adverse events in patients with impaired renal function.

The incidence of adverse events did not increase in patients with impaired renal function.

As described in the pharmacokinetic section, the total exposure with methylnaltrexone was almost doubled in patients with moderately impaired renal function. The incidence of adverse events did not increase in patients with severely impaired renal function. As a result, the applicant's proposal to half the dose in patients with severely impaired renal function was considered acceptable.

#### **Hepatic impairment**

As demonstrated in study MNTX 1107, hepatic impairment had no clear effect on the PK of methylnaltrexone. ALT and AST increased in one of eight patients with mild hepatic impairment. Adverse events data of the methylnaltrexone exposure pool were not provided.

### **Other special populations**

Age, gender, and underlying disease had no significant influence on the frequency and severity of adverse events.

- **Safety related to drug-drug interactions and other interactions**

Please see the Clinical Pharmacokinetic section for the principal conclusions regarding drug interactions.

- **Discontinuation due to adverse events**

Adverse events were cited as the reason for discontinuation in 2.4% of the placebo-treated patients and 1.5% of the methylnaltrexone-treated patients within the double blind pool. In the methylnaltrexone exposure pool adverse events were cited as the reason for discontinuation in 3.6% of the patients.

The most common reason for premature discontinuation was death. The reason for death was in general the progressive underlying disease in this population with a life expectancy of less than 6 month. The only adverse event that led to discontinuation in more than one patient was abdominal pain.

- **Post marketing experience**

Methylnaltrexone bromide has never been marketed. Therefore, no post-marketing data are available.

- **Discussion on clinical safety**

The safety outstanding issues outlined below (concerning the maximum recommended dose, the possibility of self-administration, and the occurrence of watery stools) were considered during the evaluation procedure, requesting further clarification from the applicant. They were re-solved as follows:

- Maximum recommended dose: A total of 155 subjects received consecutive daily doses of MNTX. Because of the therapeutical dilemma – no bowel movement following the first administration of MNTX and concomitant standard laxative treatment in a palliative care setting - the applicant's position that patients may receive two consecutive doses 24 hours apart was considered acceptable, but only in exceptional circumstances (only when there has been no bowel movement response to the dose on the preceding day). It was agreed that the interval of 48 hours between doses should be adhered to thereafter, and that daily use should be discouraged. This information is clearly reflected in the SPC.

The applicant submitted a summary of the safety and tolerability and of the treatment-emergent adverse events occurring in patients receiving consecutive doses of MNTX in the pivotal studies. Overall, there was no increase of the incidence of treatment-emergent adverse events in patients receiving a consecutive dose, both in study 301/301 EXT and study 302/302 EXT. Gastrointestinal disorders were also comparable. Serious adverse events in patients who received consecutive day dosing in these studies did not seem to be related to the frequency of administration. However, it was noted that one patient received MNTX on 4 consecutive days, and this is to be discouraged.

- Regarding a possible self administration of the compound, the applicant was asked to clarify what educational programme/documentation (apart from the instructions already included in the SPC) is to be used to educate the patients and healthcare professionals, and was asked to provide samples of these material. The applicant was also asked to further describe whether the product will be available with a conventional needle or with a retractable one.

The applicant provided satisfactory clarifications on the product's packages that are to be made available and on the safety mechanism of the single use syringe to be used. Clarifications were provided also on the launch and pre-launch activities foreseen.

The applicant's proposal was considered acceptable. All advertising and patient information material will be vetted upon approval. In addition, the notion that this product is for use in palliative care only will be made clear.

- Following the CHMP request at day 120 of the procedure, the applicant presented additional data regarding the occurrence of watery stools, comparing placebo and active treatment. A differential evaluation according to MNTX dose was also requested, in order to allow for the evaluation of a possible dose-response relationship.

Data on whether there was a dose effect on the production of watery stools in the MNTX studies were assessed from the following 4 sources: MNTX 301 (double-blind), MNTX 302, MNTX 301 (open-label) and MNTX 301 EXT, and MNTX 302 EXT.

Overall, across all studies, there was no meaningful dose effect in the production of watery stool, with the possible exception of the first dose. In particular, the data of study 302 EXT (table below), including nearly 2500 bowel movements, demonstrated that the occurrence of watery stool is independent of the MNTX dose.

**Table 19:** Occurrence of watery stool in Study MNTX 302.

**Subjects Who Reported Watery Stool at Any Time Prior to Next Dose By Randomized Treatment Group in MNTX 302**

0302_Ext_BM Patients who reported watery stool of any dose by Randomized Treatment Group					
MNTX 0.075		MNTX 0.15		MNTX 0.3	
Number of BM*	Number of Watery BM	Number of BM*	Number of Watery BM	Number of BM*	Number of Watery BM
65	6 ( 9.23%)	1771	168 ( 9.49%)	655	49 ( 7.48%)

## 2.5 Pharmacovigilance

### Detailed description of the Pharmacovigilance system

The CHMP considers that the Pharmacovigilance System as described by the applicant fulfils most of the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union.

### Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

The RMP provided by the MAH is considered adequate by formal criteria. Based on preclinical and clinical data the risks associated with use of RELISTOR in general seem moderate. However, the patient pool on which this estimation is based is rather small. Therefore, amendments of the RMP were considered.

As potential risks requiring further evaluation the applicant has identified the following:

- **Potential for off-label use** [rationale: the population of patients requiring chronic opioid treatment (e.g. chronic pain patients, etc) exceeds the population indicated for use of methylnaltrexone. This situation will facilitate the off-label use of methylnaltrexone]
- **Potential for misuse** [rationale: opioid drug addicts with constipation may benefit from methylnaltrexone-treatment, and therefore may be treated off-label with methylnaltrexone]
- **Potential for medication error** [rationale: the application form (subcutaneous injection) and the conditions of its use (palliative home care, etc.) may facilitate the occurrence of medication errors with methylnaltrexone, especially false intravenous injections and overdosing]

The identified and potential risks described by the applicant, as well as the methods proposed in order to monitor and minimize these risks, are considered adequate.

Table Summary of the risk management plan:

<b>Safety issue</b>	<b>Proposed pharmacovigilance activities (routine and additional)</b>	<b>Proposed risk minimisation activities (routine and additional)</b>
Gastrointestinal events	<p>Routine pharmacovigilance</p> <p>Active surveillance: Wyeth will conduct a Phase 4 randomized, double blind placebo controlled study of the efficacy and safety of a fixed dose of SC methylnaltrexone in patients with advanced illness and opioid induced constipation. (3200K1-4000-WW) as well as a randomized, double blind, placebo-controlled, parallel group study of SC methylnaltrexone for the treatment of opioid-induced constipation in subjects with chronic non-cancer pain. (3200K1-3356-WW)</p>	<p>SPC section 4.8 Undesirable effects informs that the most common adverse event in the clinical trials were gastrointestinal events.</p> <p>Given the mechanism of action, and the desired effect of methylnaltrexone, such events would be expected.</p>

**Table 6-1: EU Risk Management Plan (Cont'd)**

<b>Safety concern</b>	<b>Proposed pharmacovigilance activities (routine and additional)</b>	<b>Proposed risk minimisation activities (routine and additional)</b>
Off-label use	<p>Routine pharmacovigilance</p> <p>Active surveillance: Wyeth will collect safety information in patients in planned and ongoing clinical trials in additional indications. As part of the pharmacovigilance plan, Wyeth plans to study the safety of methylnaltrexone in additional indications and formulations including acute and chronic pain as follows: SC: OIC in patients with advanced illness, chronic non-cancer pain, and other acute populations (rehabilitation patients)  IV: management (prevention and treatment) of post-operative ileus (POI)  PO: OIC in chronic pain patients  Additional pharmacovigilance: Two drug utilisation studies will be conducted in the US and EU after marketing.</p>	<p>SPC section 4.1 Therapeutic indication explicitly states the indication and appropriate patient population for use of the SC formulation.</p> <p>SPC section 4.4 Special warnings and precautions for use recommends against use in patients with constipation not related to opioid use.</p> <p>Sales force detailing and journal advertisements will address specific messages to appropriate healthcare providers regarding indication and populations for use.</p>

**Table 6-1: EU Risk Management Plan (Cont'd)**

<b>Safety concern</b>	<b>Proposed pharmacovigilance activities (routine and additional)</b>	<b>Proposed risk minimisation activities (routine and additional)</b>
Misuse	Routine pharmacovigilance  Risk Evaluation: Consult with experts in the fields of opioid addiction and narcotic diversion to determine if there is a potential for misuse that would require enhanced risk minimisation activities.	SPC section 4.1 Therapeutic indication explicitly states the indication and appropriate patient population for use of the SC formulation.  Since the available formulation will be SC, it is unlikely that there will be widespread distribution or diversion for misuse.  Additional risk minimisation activities may be developed based on recommendations of experts.
Medication errors	Routine pharmacovigilance	SPC section 4.2 Posology and method of administration clearly outlines the dose and instructions for injection.  Patient Leaflet explicitly outlines the instructions for administering methylnaltrexone SC.  Special packaging for home care use  Patient instructions (e.g., dosing and administration card, checklist)  Dear Health Care Provider letter  Internal communication  Two fixed doses covering broad weight bands  Development of pre-filled syringes

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

## **2.6 Overall conclusions, benefit/risk assessment and recommendation**

### **Quality**

The finished product was developed as a solution for injection for subcutaneous use. The aim of the pharmaceutical development was to obtain a stable product at room temperature.

At the time of the CHMP opinion, there were minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

## **Non-clinical pharmacology and toxicology**

Overall the primary PD studies provided adequate evidence that methylnaltrexone bromide effectively antagonises the opioid-induced inhibition of gastrointestinal function, with generally no effect on the opioid-induced analgesia.

PK data revealed that bioavailability was essentially complete after s.c. dosing and very low after oral administration. RELISTOR showed a moderate to high plasma clearance compared to liver blood flow and apparent volume of distribution. The highest concentration of RELISTOR in tissue was reached within 1 hour, with small intestine, liver and kidney with the highest and brain with the lowest concentration. Afterwards the concentration in most tissues decreased, although the tissue-to-plasma ratios increased for 12 hours, indicating much faster plasma than tissue clearance. RELISTOR binding to plasma proteins was shown to be minimal. In all species investigated metabolism was limited, with the main compound in excreta being RELISTOR. RELISTOR was excreted via faeces and urine in all species after oral and systemic administration. It was shown that RELISTOR is a substrate of the human organic cation transporters. Although RELISTOR is a relevant substrate of CYP 2D6 and the human organic cation transporters, no clinically relevant interactions with these drugs were assumed.

General signs of toxicity reported during toxicology studies were abnormal gait and stance, low carriage, body tremors and labored respiration. The single dose toxicity studies exhibited a relatively low acute toxicity. The main clinical signs of RELISTOR exposure at high doses in the repeat dose toxicity studies were tremors, convulsion, decreased activity, abnormal stance and gait, and prostration in rats as well as in dogs. In addition, in dogs also ptosis, bloodshot eyes, protruding nictitating membranes, dilated pupils and absence of menstrual cycling were apparent.

No changes of macroscopic, microscopic and clinical chemistry parameters were described.

The studies performed did not bring evidence for clinically relevant genotoxic potential of RELISTOR. Milk and placental transfer of RELISTOR were shown after subcutaneous administration in rats; in this species high doses of RELISTOR also appeared to impair fertility.

No separate local tolerance studies were performed; the studies performed with subcutaneous administration showed an acceptable local tolerance, although a significant influence of the formulation was demonstrated in the repeated dose studies.

In conclusion, the use of RELISTOR was not considered to pose a risk to the environment.

## **Efficacy**

Results from the pivotal studies performed showed the clear superiority of RELISTOR over placebo in the induction of prompt laxation in patients that are already treated with laxatives for opioid induced constipation and have ongoing difficulties with defecation.

Laxation within 4 hours after the first dose of study drug was observed in 48.4% (CI = 35.9-60.8) of patients in the RELISTOR group versus 15.5% (CI = 7.1-23.9) of patients in the placebo group. The proportion of patients with  $\geq 2$  laxations within 4 hours after dose administration over the first 4 doses was 51.6% (CI = 39.2-64.1) in the RELISTOR group and 8.5% (CI = 2.0-14.9) in the placebo group. The secondary endpoints were generally in support of the primary endpoints.

It was recognised that the population investigated was rather small, and that also the duration of the double-blind phases of the performed studies was limited.

In addition, there was some indication that the compound relieves defecation complaints and improves stool consistency over the short term, leading to an overall patient satisfaction that is clearly distinct from placebo.

Open label extension studies showed that the a.m. effects can be maintained up to three months.

## **Safety**

Data provided on adverse events were limited. The rate of adverse events within the system organ classes 'Gastrointestinal disorders' and 'Nervous system disorders' (i.e. abdominal pain, flatulence, diarrhoea, nausea, and dizziness) was higher in the methylnaltrexone group than in the placebo group.

Serious adverse events occurred in 19.9% of the overall population of patients exposed to RELISTOR. In the double-blind treatment pool the frequency of serious adverse event was 8.9% for placebo and 2.5% for RELISTOR.

The most commonly reported events were abdominal pain, nausea and vomiting and flatulence. The healthy volunteer subjects investigated did not show any serious adverse event. The frequency of serious adverse events was relatively low with regard to the special study population with a life expectancy lower than 6 months.

The incidence of adverse events did not increase in patients with impaired renal function. The total exposure with RELISTOR resulted almost doubled in patients with moderately impaired renal function. The incidence of adverse events did not increase in patients with severely impaired renal function. From the data provided, no clear effect of hepatic impairment on the PK of RELISTOR could be observed. Finally age, gender and underlying disease had no significant influence on frequency and severity of adverse events.

### **Benefit/risk assessment**

RELISTOR clearly showed that a prompt induction of laxation is possible in patients with opioid induced constipation still having significant constipation problems on top of “usual” laxative treatment. This was shown to improve patient satisfaction with defecation habits, to improve stool consistency to some extent, and possibly also to relieve some of the associated symptoms. There was also some indication that the use of rectally administered laxatives can be reduced compared to placebo. Moreover, explorative analysis showed that the compound was also able to relieve constipation in a “conventional” sense with a composite beneficial influence on stool consistency, stool frequency, and defecation difficulties in patients with a high degree of constipation. However, a possible reduction of overall “usual laxative medication” could not convincingly be shown. As a result, the proven benefits of the compound appeared to be limited to some extent.

The number of patients treated with RELISTOR in clinical studies was limited, and only very few patients were treated with the product for more than 4 weeks. In addition, the patients included in the clinical studies had a life expectancy between 1 and 6 month with the consequence of a very high withdrawal rate due to death.

The administration of RELISTOR for the short term treatment of constipation in patients with a life expectancy between 1 and 6 month seemed to be safe. The adverse events referred particularly to the gastrointestinal tract (e.g. abdominal pain, nausea) and the nervous system (e.g. dizziness) and were in general mild or moderate in severity.

Safety data of long term treatment were missing and therefore the treatment with RELISTOR should be restricted to the patient population evaluated in clinical studies (that is mentioned above).

The applicant identified a potential off-label use, potential misuse and possible medication errors to be potential risks that require further evaluation. The potential risks identified and described by the applicant, as well as the methods proposed in order to monitor and minimize these risks, were considered adequate.

The benefits of the treatment, being rather symptomatic in nature, were considered to be sufficient for approval because the risks appeared to be limited, especially regarding serious and severe undesirable effects. Although the number of patients evaluated was small and the treatment duration was limited, adequate measures were proposed to ensure that the compound is only used for no longer than 3 months, and in the investigated patient population only. The Risk-Benefit balance was therefore considered positive.

### **Recommendation**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the benefit/risk ratio of RELISTOR in the “treatment of opioid-induced constipation in advanced illness patients who are receiving palliative care when response to usual laxative therapy has not been sufficient” was favourable and therefore recommended the granting of the marketing authorisation.