EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 April 2015
EMA/300379/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Relistor

International non-proprietary name: METHYLNALTREXONE BROMIDE

Procedure No. EMEA/H/C/000870/II/0030

Note

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

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List of abbreviations

Abbreviation or specialist term	Explanation
AE	Adverse event
AUC	Area under the concentration-time curve
AUC_{∞}	Adjusted area under the concentration-time curve from time zero to infinity
AUC_{SS}	Area under the concentration-time curve at a steady state
$AUC_{SS, \tau}$	Area under the concentration-time curve within a dosing interval at steady state
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (The Federal Institute for Drugs and Medical Devices)
BSS	Bristol Stool Form Scale
Cl	Clearance
C_{max}	Maximum observed concentration
CPMP	Committee for Proprietary Medicinal Products
CSR	Clinical study report
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCIC	Global Clinical Impression of Change
GCP	Good Clinical Practice
GI	Gastrointestinal
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
IV	Intravenous
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MACE	Major Adverse Cardiovascular Event
MAH	Marketing Authorisation Holder
mITT	Modified intent-to-treat
MNTX	Methylnaltrexone bromide
NDA	New Drug Application
OIC	Opioid-induced constipation
OOWS	Objective Opioid Withdrawal Scale
PAC-QOL	Patient Assessment of Constipation – Quality of Life
PAC-SYM	Patient Assessment of Constipation – Symptoms
PK	Pharmacokinetics
PRN	As needed
PT	Preferred term
QD	Once daily
QOD	Once every other day
QoL	Quality of Life
RFBM	Rescue-free bowel movement

SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SmPC	Summary of Product Characteristics
sNDA	Supplemental New Drug Application
SOC	System Organ Class
SOWS	Subjective Opioid Withdrawal Scale
TEAE	Treatment-emergent adverse events
US	United States (of America)

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, TMC Pharma Services Ltd submitted to the European Medicines Agency on 13 March 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product(s): **For presentations: See Annex A**	**International non-proprietary name**
Relistor	METHYLNALTREXONE BROMIDE

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

The MAH applied for an extension of the indication for the treatment of opioid induced constipation in adult non cancer patients. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4 and 5.1 of the SmPC. The Package Leaflet was proposed to be updated in accordance.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

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

Additional data protection/marketing exclusivity

The applicant requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The applicant did not seek scientific advice and Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Harald Enzmann Co-Rapporteur: Greg Markey

Timetable	Dates
Submission date	13 March 2014
Start of procedure:	28 March 2014
CHMP Rapporteur Assessment Report	19 May 2014
PRAC Rapporteur Assessment Report	21 May 2014
PRAC Rapporteur Updated Assessment Report	02 June 2014
Rapporteur Revised Assessment Report	23 June 2014
Request for supplementary information (RSI)	26 June 2014
CHMP Rapporteur Assessment Report	26 October 2014
PRAC Rapporteur Assessment Report	20 October 2014
Committees comments on PRAC Rapp Advice	26 October 2014
PRAC Rapporteur Updated Assessment Report	29 October 2014
Rapporteur Revised Assessment Report	12 November 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	06 November 2014
CHMP comments	10 November 2014
2nd Request for supplementary information (RSI)	20 November 2014
CHMP Rapporteur Assessment Report	19 February 2015
PRAC Rapporteur Assessment Report	23 February 2015
Rapporteur Revised Assessment Report	18 March 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	12 March 2015
3rd Request for supplementary information (RSI)	26 March 2015
PRAC Rapporteur Assessment Report	08 April 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	10 April 2015
CHMP Rapporteur Assessment Report	14 April 2015
Opinion	23 April 2015

2. Scientific discussion

2.1. Introduction

Methylnaltrexone bromide is a quaternary derivative of the μ-opioid antagonist, naltrexone. Whereas naltrexone is used to counteract the CNS related effects of opioid treatment (including overdose), Methylnaltrexone bromide was designed to block the undesired peripheral side effects of opioids without interfering the central analgesic effects.

Activation of μ-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 Methylnaltrexone bromide as a peripheral μ-opioid receptor antagonist to counteract opioid induced constipation is the pharmacodynamic rationale.

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. 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.

Relistor (methylnaltrexone bromide) s.c. was licenced in the EU in July 2008

- for the treatment of opioid-induced constipation in advanced illness for patients receiving palliative care when response to usual laxative therapy has not been sufficient.

These patients with “end stage disease with limited life-expectancy” represented mostly cancer pain patients.

This application is for the extension of the indication to treat patients with opioid-induced constipation with non-cancer pain. The proposed wording of the additional indication is as follows:

Relistor is indicated for the treatment of opioid-induced constipation in adult patients, aged 18 years and older, with chronic non-cancer pain.

The finally approved indication was summarised together with the existing indication to:

Relistor is indicated for the treatment of opioid-induced constipation when response to laxative therapy has not been sufficient in adult patients, aged 18 years and older.

No Scientific Advice has been received through centralised procedure for this proposed extension of indication. At submission of the dossier no specific guidance was available for the indication opioid-induced constipation (OIC).

2.2. Non-clinical aspects

2.2.1. Introduction

Repeated dose toxicity studies in mice, rats and dogs of up to 3, 6 and 9 months, respectively as well as 2 year carcinogenicity studies in mice and rats were already part of the existing non-clinical data package and no further studies were needed in support of this extension of the patient population to non-cancer patients.

The MAH submitted with this application for extension of the indication to adult non-cancer patients the documentation of a total of 7 new non-clinical studies. These consist of one primary and one secondary in vitro pharmacology study, two in vitro metabolism studies, one in vitro metabolism/distribution study, one analytical method validation report provided in the pharmacokinetics section and one analytical method validation report provided in the toxicology section.

2.2.2. Pharmacology

Primary pharmacodynamic studies

MNIV0101 [The Effects of Methylnaltrexone, 6-Alpha-Methylnaltrexol, 6-Beta-Methylnaltrexol and 3-Sulfo-Methylnaltrexone in *In Vitro* Human μ-, κ-, and δ-Opioid Receptor Binding Assay].

The study aimed at evaluation, in radioligand binding assays, of the activity of MNTX, 6-alpha-methylnaltrexol (M4), 6-beta-methylnaltrexol (M5) and 3-sulfo-methylnaltrexone (M2) at the human μ-, κ-, and δ-opioid receptor expressed in mammalian cell lines.

MNTX and its metabolites demonstrated binding to the human μ-opioid receptor expressed in CHO-K1 cells with the following IC_{50} rank order of potency: M4 (34 nM) > MNTX (100 nM) > M5 (190 nM) >> M2 (10.7 μM) (The corresponding Ki values were determined as 14 nM [M4], 42 nM [MNTX], 78 nM [M5] and 4.33 μM [M2]). MNTX, M4 and M5 demonstrated similar binding to the human κ-opioid receptor expressed in HEK293 cells (IC_{50} values of 510 to 590 nM), while M2 had limited binding to the κ-opioid receptor, with an IC_{50} value of 21.4 μM. MNTX, M4, M5 and M2 had limited binding to the δ-opioid receptor with IC_{50} values of 33.1 μM, 32.6 μM, 45.6 μM, and >100 μM, respectively.

Secondary pharmacodynamic studies

MNIV0102 [The Effect of Methylnaltrexone, Naloxone and Naltrexone on Platelet Aggregation in Human Platelet Rich Plasma].

The ability of MNTX, naltrexone and naloxone to affect platelet aggregation *in vitro* was investigated using human platelet rich plasma. MNTX, naloxone, and naltrexone did not induce platelet aggregation at either concentration tested (0.5 and 500 μM for naltrexone and naloxone, and 0.6 and 612 μM for MNTX). Inhibition of platelet aggregation was investigated using 4 substances that induce platelet aggregation: Adenosine diphosphate (ADP), arachidonic acid, platelet activating factor (PAF), and the stable thromboxane analog, U-46619. At the higher concentration, all three compounds exhibited inhibition of platelet aggregration. Inhibition of PAF-induced platelet aggregation was the most affected by MNTX, naloxone, and naltrexone. Naloxone (500 μM) inhibited PAF-induced platelet aggregation by 68%, naltrexone (500 μM) inhibited by 49%, and MNTX (612 μM) inhibited PAF-induced platelet aggregation by 37%.

2.2.3. Pharmacokinetics

Methods of analysis

RPT-73085 [MOA-728: Long Term Storage Stability of MOA-728 in Dog Plasma]

To evaluate the stability of MOA-728 in dog plasma, plasma samples spiked with 3 and 400 ng/mL MOA-728 were stored for 201 days at -70°C. Samples were analysed at day 0, 10 and 210 for MOA-728 concentration using a validated LC/MS/MS method. The results showed that MOA-728 is stable under the indicated conditions.

Distribution

XT128007 [In Vitro Evaluation of Methylnaltrexone as an Inhibitor of Human P-gp, BCRP, OCT2 and MRP2 and Substrate of Human BCRP, MRP2, OATP1B1, OATP1B3, OAT1 and OAT3 Transporters]

The ability of MNTX to inhibit P-gp and BCRP was evaluated by measuring the bidirectional permeability of a probe substrate across a monolayer of Caco-2 cells or MDCKII-BCRP cells in the presence of MNTX. Inhibition was assessed for MRP2 in membrane vesicles by measuring the effect of MNTX on the accumulation of a probe substrate in the vesicles, and for OCT2 in HEK293 cells by measuring the effect of MNTX on the accumulation of a probe substrate in the cells. To evaluate whether MNTX was a substrate of the human efflux transporter BCRP, the bidirectional permeability of MNTX was measured across MDCKII-BCRP and MDCKII control cells, and for the efflux transporter MRP2, by measuring the accumulation of MNTX in transporter expressing and control vesicles. To assess whether MNTX was a substrate of human uptake transporters, the accumulation of MNTX was measured in transporter expressing and control cells (HEK293cells for OATP1B1 and OATP1B3, and S2 cells for OAT1 and OAT3). Known inhibitors were included as positive controls in all experiments. In vitro , MNTX did not inhibit human P-gp or BCRP transporters at concentrations between 5 µM and 500 µM. OCT2 was inhibited 48.4% in the presence of the highest concentration of MNTX (100 µM). MNTX was not a substrate of BCRP in MDCKII-BCRP cells, and did not accumulate in vesicles expressing MRP2, or in cells expressing OATP1B1, OATP1B3, OAT1, or OAT3, which suggests that MNTX is not a substrate of these transporters.

2.2.4. Toxicology

Other toxicity studies

Covance 8220358 [Validation of a Method for the Determination of RRT 0.60 in Rat Plasma by HPLC with MS/MS Detection]

The objective of this study was to validate a method for the determination of RRT 0.60 (a degradant of MNTX, also known as WYE-129943) in rat plasma with K2EDTA as an anticoagulant by HPLC with MS/MS detection. RRT 0.60 and the internal standard (ISTD), MNTX bromide (N-methyl-13CD3), were extracted from samples by protein precipitation. After evaporation under nitrogen, the residue was reconstituted [0.5% formic acid in (10:90, v:v) methanol:water] and analysed using liquid chromatography with tandem mass spectrometric detection. The lower limit of quantitation (LLOQ) for RRT 0.60 in rat plasma was 10.0 ng/mL, with linearity demonstrable to 1000 ng/mL (upper limit of quantitation, ULOQ), using a sample volume of 50.0 µL. Results were calculated using peak area ratios of analyte to ISTD, and calibration curves were generated using a weighted (1/x2) linear least-squares regression. The precision

and accuracy results for the quality control (QC) samples were within acceptance criteria, and it was therefore concluded that the method demonstrated acceptable precision and accuracy. Stability of RRT 0.60 and MNTX bromide (N-methyl- 13CD 3) under a variety a variety of conditions. A quantitative procedure for the determination of RRT 0.60 in rat plasma, over the concentration range of 10.0 to 1000 ng/mL, was successfully validated for use at Covance. The method utilised a sample volume of 50.0 µL.

2.2.5. Ecotoxicity / environmental risk assessment

The PEC for the indication palliative care was 0.00096 µg/l and no Phase II ERA was necessary. The new indication leads to a clear increase in the number of patients treated. Methylnaltrexone bromide has a log Kow of -1.605. The percentage of people 18 years and older is 80 %. Based on Panchal et al. 2007, chronic pain of moderate to severe intensity occurs in 19 % of adults. 5 % use strong opioids. Panchal et al. 2007 state that "*Estimates of the frequency of constipation vary from 15–90% in patients receiving opioids for noncancer pain*". Other references, e. g. NHS 2012, Kalso et al. 2004, and Camilleri, 2011 all report frequencies around 40 %.

As there is variation in the frequency of constipation reported in different studies, the frequency of constipation cannot be taken into account for PEC refinement. Even if only 25 % of the patients treated would suffer from constipation, the PEC surface water would be higher than the action limit 0.01 µg/l.

The refined $PEC_{surface\ water}$ for the additional indication (chronic non-cancer pain) is 0.042. The resulting PECsurface water for Relistor is 0.043 which is higher than the action limit.

As a result of the above considerations, the available data do not allow exclude definitively a risk of Methylnaltrexone bromide to the environment.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed: To submit a Type II ERA.

2.2.6. Discussion on non-clinical aspects

The newly submitted in Vitro Human µ-, κ-, and δ-Opioid Receptor Binding Assay (MNIV0101) determines for the rank order of potencies M4 as being more potent than the parent compound MNTX itself. However, as per data previously submitted, the ratio of total ($AUC_{metabolite}/AUC_{parent}$) systemic exposures of the most abundant metabolites relative to the parent compound (223 ng·h/mL) at steady state were approximately 29.3% for M2, 18.8% for M4, and 8.7% for M5 and the lower circulating levels of M2, M4 and M5 affirm that MNTX is the primary agent responsible for the observed pharmacological activity. The M2 metabolite was only weakly active as a µ-opioid receptor antagonist (1000-fold less than M4 or M5). In human platelet rich plasma inhibition of PAF induced platelet aggregation by 37% was observed in MNTX concentration of 612 µM. As the human therapeutic Cmax of 329 nM (117 ng/mL) is less than 1/1000 of that and as the lower concentration of 0.6 µM [= 600 nM] only lead to an inhibition of 5% this findings are considered to be without clinical relevance.

The influence of MNTX on several human drug transporters was investigated in an in-vitro test system (study (XT128007). With the exception of OCT2 no interactions were noted. OCT-related drug-drug interaction potential is already reflected in the SmPC.

2.2.7. Conclusion on the non-clinical aspects

No additional non-clinical studies were necessary in support of the new indication. Therefore the newly submitted studies add only to the completeness of the data package. Dosing schedule and drug exposure are unaffected within the change in the patient population and the wording of SmPC section 4.6 fertility, pregnancy and lactation and 5.3 preclinical safety data and PIL section 2 on pregnancy and lactation remains unchanged.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation: To perform a Type II ERA.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1: Overview on PK studies presented in support of the variation:

Study code (Abrreviation)	Country of conduct	Test product/ Route of administration	Objective	Subjects/No.
1109-SC (**1109)**	USA	MNTX 12 mg; S.C.	Single and Multiple dose PK and metabolites.	HVs (10 f; 10 m) mean age 32.8 yr
3200A3-105-US (**105**)	USA	0.15 mg/kg S.C.; 300 mg orally	Comparison of relative bioavailability of oral capsule formulation to tablet formulation; PD effect of SC (single dose of 0.15 mg/kg to oral administration) 300 mg)	HVs ; n=40; aged 22-54.
3356 (**3356)**	USA, Canada	MNTX 12 mg; S.C. QD or QOD	Safety and efficacy	PK population: 25 m; 15 f, mean age: 49.0 yr
1303 (**1303**)	USA	MNTX 24 mg q6h IV	Effect of age on MNTX PK	14 young adult, 14 elderly (65-84 yr); 12 m; 7 f.
1304 (**1304**)	USA	MNTX 24 mg (two single doses); IV	Effect of cimetidine on MNTX PK	HVs, mean age 28.1 yr; 17 m, 1 f.

Table 2: Overview on clinical studies

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
2101	USA 19	Ph 2, rand. DB, parallel-group Pl.-control	MNTX SC 12 mg once daily Placebo	Activity PK/PD safety	18/15 MNTX 15/12 placebo	4-7 days	11/22 62 yrs.	Patients in rehab after orthopaedic surgery	Safety; RFBM within 2 h and 4 h after first dose; proportion of injections with RFBM within 2h and 3 h after dosing; time to RFBM.
3356	USA, Canada 91	Ph 3; rand. Parallel-group, DB, placebo-controlled	MNTX 12 mg SC daily, MNTX 12 mg SC every other day Placebo	Efficacy, Safety and Tolerability	150/122 148/120 162/146 Open label: 364/303	4 weeks double-blind; 8 weeks open-label	183/277 49 yrs. (23-83)	Pat. With non-cancer pain who have OIC; history of OIC at least 1 mo. before screening	Co-primary: % of patients having RFBM within 4 h of first dose % of active injections resulting in RFBM within 4 h after dose
3358	USA, Canada, Australia, Spain, Korea, Colombia	Ph. 3 Open-label	MNTX SC 12 mg OD or as needed (but at least once weekly	Long-term safety and tolerability	1034/477	48 weeks	365/669 52 yrs. (23-81)	Pat with chronic non-cancer pain who have OIC History of OIC for at least one month	Safety. Secondary efficacy: BMs per week, " of injections resulting in BM within 4 h; BSS, Straining Scale, Completeness of Evacuation

2.3.2. Pharmacokinetics

Absorption

Study 1109

Study 1109 was a phase 1, multiple dose, open-label study to evaluated the PK of methylnaltrexone in healthy adults subjects. The study included 10 male and 10 female healthy volunteers aged between 18 and 47 years of age. The primary objective of the study was to evaluate the PK profile of 12 mg MNTX and its M2, M4, and M5 metabolites when MNTX was administered as an SC injection once daily for seven days in healthy adults subjects.

The main results of the study are shown in the following tables, showing the PK parameters for MNTX, as well as the three main metabolites tested:

Table 3: PK parameters (mean and (SD) for MNTX and its metabolites following single SC dose of MNTX 12 mg to healthy subjects:

Parameters	MNTX (N=20)	M2 (N=20)	M4 (N=20)	M5 (N=20)
C_{max} (ng/mL)	140 (35.6)	6.34 (2.66)	4.64 (2.14)	1.17 (0.554)
T_{max} (h)	0.29 (0.09)	4.30 (1.49)	1.13 (0.56)	2.73 (2.00)
AUC_t (ng*h/mL)	218 (28.3)	58.8 (23.2)	34.7 (11.1)	14.4 (4.54)
AUC_∞ (ng*h/mL)	223 (29.1)	71.9 (23.3)[a]	38.3 (10.6)[b]	18.5 (6.55)[c]
AUC_{0-24} (ng*h/mL)	218 (28.3)	63.1 (21.0)	34.7 (11.1)	14.4 (4.54)
$t_{1/2}$ (h)	5.43 (0.755)	6.08 (1.50)[a]	7.79 (1.33)[b]	8.36 (1.48)[c]

Reference: Study MNTX 1109 CSR, Table 11.
AUC=area under the curve; AUC_∞=AUC from time zero to infinity; AUC_{0-24}=AUC from time zero to 24 hours; AUC_t=AUC from time zero to the last quantifiable concentration; C_{max}=peak plasma concentration; M2=3-sulfo methylnaltrexone; M4=methyl-6α-naltrexol; M5=methyl-6β-naltrexol; SC=subcutaneous; SD=standard deviation; $t_{1/2}$=terminal elimination half-life; T_{max}=time to peak plasma concentration.
[a] N=16
[b] N=14
[c] N=8

Table 4: PK parameters (man and (SD)) for MNTX and its metabolies following multiple SC doses of MNTX 12 mg to healthy subjects:

Parameters	MNTX (n=17)	M2 (n=17)	M4 (n=17)	M5 (n=17)
C_{max} (ng/mL)	119 (27.2)	5.70 (1.32)	4.33 (1.55)	1.42 (0.444)
T_{max} (h)	0.31 (0.11)	4.82 (1.88)	1.47 (0.86)	2.76 (1.44)
AUC_t (ng*h/mL)	223 (28.2)	61.3 (21.3)	41.9 (13.5)	19.5 (6.26)
AUC_{0-24} (ng*h/mL)	223 (28.2)	66.3 (16.7)[a]	41.9 (13.5)	19.5 (6.26)
R (%)	105 (6.43)	116 (16.4)	125 (18.3)	142 (24.4)

Reference: Study MNTX 1109 CSR, Table 13.
AUC=area under the curve; AUC_t=AUC from time zero to the last quantifiable concentration; AUC_{0-24}=AUC from time zero to 24 hours; C_{max}= peak plasma concentration; M2=3-sulfo methylnaltrexone; M4=Methyl-6α-naltrexol; M5=Methyl-6β-naltrexol; SC=Subcutaneous; R=accumulation index; SD=standard deviation; T_{max}=time to peak plasma concentration.
[a] N=16

No relevant accumulation of MNTX was found (accumulation index [R] = 105%) following SC dosing for seven consecutive days. _The accumulation factors of the metabolites M2, M4, and M5 were higher with 116%, 125%, and 142%, but still regarded to be minimal overall. The higher accumulation factors are consistent with the longer half-lifes of the metabolites.

The study concludes that MNTX was rapidly absorbed after single and multiple SC dosing with a mean T_{max} of 0.3 hours. Time to reach peak exposure was higher for the metabolites.

Study 105

The study with the title “A randomised, open-label, three-period crossover study to determine the relative bioavailability of two oral formulations of MOA-728 and to compare the pharmacodynamics of the two oral formulations of MAO-728 to the subcutaneous formulation in subjects on stable methadone maintenance” was conducted between November 2006 and December 2006. The following results were achieved:

Table 5: Summary of mean PK parameters for MNTX after administration of SC MNTX 0.15 mg/kg in subjects on stable methadone maintenance and of two oral formulations.

Treatment/ Dose	C_{max} (ng/mL)	t_{max} (h)	AUC_{∞} (h*ng/mL)	$t_{1/2}$ (h)	Cl/F (L/h/kg)	%F*
SC/	188 ± 48	0.5	307 ± 126	11.4 ± 5.7	0.55 ± 0.18	-
0.15 mg/kg	(118, 326)	(0.5, 0.6)	(172, 711)	(4.5, 27.7)	(0.21, 0.87)	
Capsule/	31.5 ± 19.8	3.1	172 ± 89	33.3 ± 18.6	25.8 ± 12.4	2.43 ± 0.84
300 mg	(10.4, 71.5)	(3.1, 8.0)	(78.2, 462)	(11.0, 80.0)	(7.5, 51.2)	(0.73, 3.93)
Tablet/	22.6 ± 14.2	3.1	156 ± 69	27.5 ± 14.6	31.0 ± 26.4	2.27 ± 1.00
300 mg	(1.8, 55.6)	(1.0, 24.0)	(29.7, 299)	(8.6, 61.7)	(10.9, 135)	(0.52, 4.33)

Abbreviations: AUC=area under the concentration-time curve; Cl=clearance; Cl/F=oral dose clearance; C_{max}=peak concentration; t_{max}=time to peak concentration; $t_{½}$=terminal-phase elimination half-life; SC=subcutaneous; SD=standard deviation.

Note: Data presented are mean ± SD (min, max) except for t_{max}. For t_{max}, median (min, max)

* %F=relative bioavailability of capsule/tablet formulation compared with SC formulation.

Source path: /CLINICAL R&D/CLINICAL PHARMACOKINETICS ANOVA AND GRAPHS/3200K1 MOA-728/105/PK Tables and Figures/MOA intext PK Figures & Tables.doc.

The overall exposure appears to be higher in this patient population compared to HVs and OIC patients. There was no apparent relationship between systemic exposure to MNTX and MNTX PK parameters.

Pharmacokinetics in the target population:

Study 3356

Study 3356 was the pivotal phase III study relevant for this type II variation for the extension of the indication. The study termed “A multicentre, randomised, double-blind, placebo-controlled, parallel-group study of subcutaneous MOA-728 for the treatment of opioid-induced constipation in subjects with chronic non-malignant pain” was conducted between August 2007 and November 2008 in the USA and Canada.

During the study, blood samples were obtained at selected sites from “willing subjects” for trough and peak PK analysis. Two trough PK blood samples were collected before study drug administration, and additional peak PK blood samples were collected at baseline, at 1, 2, and 4 hours and between 6 and 12 hours after study drug administration. 43 subjects contributed PK samples. The results are shown in the following table:

Table: 5: Summary of MNTX PK parameters following a single SC dose (Day 1) in subjects with OIC.

Treatment Group	C_{max} (ng/mL)	T_{max} (h)[a]	AUC_t (ng*h/mL)
MNTX 12 mg QD (N=16)	80.7 (44.4)	1.1 (0.9, 2.0)	146 (111)
MNTX 12 mg QOD (N=24)	88.5 (51.7)	1.0 (0.0, 2.1)	183 (249)

Reference: Study 3200K1-3356-WW CSR, Table 12-1.

AUC_t=area under the curve from time zero to the last quantifiable concentration; C_{max}=peak plasma concentration; PK=pharmacokinetic(s); QD=once daily; QOD=once every other day; SD=standard deviation; T_{max}=time to peak plasma concentration

[a] Median (min, max) values are reported for T_{max}.

A daily administration dose in the target population did not lead to higher exposure (per day) compared to every other day administration. These results compared well to the exposure seen in healthy volunteers.

2.3.3. Pharmacodynamics

Mechanism of action

Methylnaltrexone bromide is a selective antagonist of opioid binding at the μ-receptor. In vitro studies have shown methylnaltrexone bromide to be a μ-opioid receptor antagonist (inhibition constant [Ki] = 28 nM), with 8-fold less potency for kappa opioid receptors (Ki = 230 nM) and much reduced affinity for delta opioid receptors.

As a quaternary amine, the ability of methylnaltrexone bromide to cross the blood-brain barrier is restricted. This allows methylnaltrexone bromide to function as a peripherally acting mu-opioid antagonist in tissues such as the gastrointestinal tract, without impacting opioid-mediated analgesic effects on the central nervous system.

2.3.4. Discussion on clinical pharmacology

The MAH has provided additional PK from 3 studies. Two (2) of these studies were dedicated PK studies, documenting PK in healthy volunteers. The third study presents the data from the PK investigations included in the pivotal phase 3 study for the extension of the indication to the non-malignant pain OIC population. Studies MNTX 1303 and 1304 were already submitted within the initial marketing authorisation and do not provide additional information.

The PK study in healthy volunteers tested single- and multiple-dose PK for the fixed dose proposed (12 mg SC). Peak and mean exposures, T_{max} and t ½ values were in the expected ranges. A relevant accumulation of the mother compound could be excluded with the minimal accumulation documented and, considering the half-lives of all four compounds being investigated (5.43 (MNTX), 6.08 (M2), 7.79 (M4), and 8.36 (M5) hours) it can be assumed that steady state had been reached by day 7. Pre-dose concentration values at Day 7 and 24 hours after last dosing did not indicate further accumulation either. Based on the observed concentrations, and the known activity of the metabolites at the μ-receptor (based on Ki), the metabolites would not contribute more than 30% of the total activity of the compound.

The sparse PK sampling from OIC patients did not reveal relevant deviations in PK in the target population.

In patients with methadone treatment plasma levels (peak and total extent of exposure) appeared to be slightly higher and the t ½ increased compared to healthy volunteers and the target population (study 105). However there was a marked overlap in range of the PK values across studies and MTNX kinetics was not dependent on methadone exposure, making a PK interaction unlikely.

In contrast to the posology for patients with advanced illness a fixed single dose for all patients (12 mg) regardless of the body weight is proposed. During the procedure the MAH presented data from 8 PK studies conducted with various doses of MNTX with dose normalisation to a fixed 12 mg dose, or the 0.15 mg/kg dose, and then compared C_{max} and AUC showing that there are only insignificant differences between the fixed dose and the body-weight related doses in weight categories above and under 60 kg. Only a slightly higher exposure of patients with less than 60 kg of body weight with the fixed dose could be shown. The CHMP therefore supports the proposed administration of a fixed dose of 12 mg.

2.3.5. Conclusions on clinical pharmacology

The presentation of the additional data does support the proposed administration of a fixed dose of 12 mg. Respective PK investigations have been performed with healthy volunteers and in patients and do show adequate exposure in the patients.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Study 2101

Study 2101 was a double-blind, randomised, parallel-group, placebo-controlled, phase 2, hypothesis-generating study designed to assess the safety and efficacy of MNTX in patients who experienced OIC during rehabilitation after orthopaedic procedures.

Eligible patients were randomised in a 1:1 ratio to receive QD SC injections of either MNTX (12 mg) or placebo for up to four or seven days. The efficacy objectives of this study were to evaluate the activity of SC MNTX 12 mg in male and female patients with OIC following orthopaedic surgery.

All efficacy endpoints were considered secondary. The proportion of patients who had an RFBM within two hours after the first dose of study medication was significantly higher in the MNTX group than in the placebo group (33% in the MNTX group versus no patients in the placebo group [p<0.05]). Similarly, a significantly greater proportion of the patients in the MNTX group had an RFBM within four hours after the first dose of study drug, compared to that in the placebo group (39% in the MNTX group versus 7% in the placebo group [p<0.05]). In addition, there was a more rapid time to first RFBM for patients treated with MNTX than for those treated with placebo, with a median time to first RFBM of 15.8 hours for the MNTX group versus 50.9 hours for the placebo group (p<0.05).

2.4.2. Main study

Study 3200K1-3356WW: A multicentre, randomized, double-blind, placebo controlled, parallel-group study of subcutaneous MOA-728 for the treatment of opioid-induced constipation in subjects with chronic non-malignant pain

Methods

Study participants

Subjects included had to have a history of chronic pain with non-malignant condition, of at least 2 months duration, taking opioids for at least 1 month and have a history of constipation for at least 1 month. The inclusion criteria were resembling the Rome III criteria for chronic constipation, although not completely similar. Relevant medical diagnoses were exclusion criteria.

Treatments

Eligible subjects who signed an ICF entered a 14-day (+ 2-day visit window) screening period, during which objective evidence of constipation was assessed. Subjects who remained eligible at the baseline visit were randomly assigned to receive daily injections containing placebo, MOA-728 12 mg daily (QD), or MOA-728 12 mg every other day (QOD) in a 1:1:1 allocation ratio. Subjects participated in a treatment period for up to 84 days including 4 weeks of double-blind QD or QOD treatment followed by 8 weeks of open-label PRN dosing. In the open-label phase, all subjects received MOA-728 12 mg. The study included a 14-day posttreatment follow-up period.

Objectives

The primary objective of the study was to evaluate the safety, efficacy, and tolerability of SC MOA-728 versus placebo in subjects with chronic nonmalignant pain who have OIC.

The secondary objective of the study was to explore subject-reported outcomes for benefits of treatment with MOA-728.

Outcomes/endpoints

The finally evaluated endpoints according to Protocol Amendment II were the following:

- The proportion of subjects having a RFBM within 4 hours of the first dose
- The percentage of active injections resulting in any RFBM within 4 hours during the double-blind phase. To qualify as a RFBM, the BM could not have occurred within 24 hours after rescue laxative administration.

The two key secondary efficacy endpoints were the following:

- The time to the first RFBM after the first injection, censored at 24 hours or time of the second injection, whichever occurred first
- The change in weekly number of RFBMs from baseline to the double-blind phase.

Other secondary efficacy endpoints included the following:

The weekly RFBM rate (other than in the DB phase), the proportion of subjects achieving at least 3 RFBMs per week, the percentage of active injections resulting in any RFBM within 1,2,3,4, and 6 hours, the percentage of (any) injections resulting in any RFBM within 1,2,4, and 6 hours, the proportion of subjects with a weekly RFBM rate of three or more and an increase of at least 1 FBM from baseline, the proportion of subjects with an increase of at least 1 in the weekly RFBM rate from baseline, the weekly BM rate, the weekly number of "quality RFBMs, i.e. the RFBMs with stool quality other than diarrhoea (BSFS 1-5), the weekly number of complete RFBMs (=with a sense of complete evacuation), the average BSFS, the average straining scale of RFBMs, the proportion of subjects with improvement in BSFS by 1 degree, the proportion of subjects with improvement in straining scale of RFBMs by 1 degree, the proportion of RFBMs with BSFS 3 or 4, with those classified as diarrhoea or watery, those with Straining Scale of 0 or 1, the percentage of RFBMs with sensation of complete evacuation, pain intensity scale, and others.

Subject-reported outcomes were measured by the PAC-QoL, the PAC-SYM, the EQ-5D and the WPAI.

Sample size

Approximately 470 subjects (157 subjects per treatment group) were to be enrolled in this study. The sample size estimation was based on the 2 co-primary endpoints and the 2 key secondary efficacy endpoints. Three (3) comparisons for the 2 co-primary endpoints were performed sequentially. A comparison between the combined MOA-728 groups (MOA-728 QD 12 mg and MOA-728 QOD 12 mg) and the placebo group was performed first using 2-sided Chi-square test for the first co-primary endpoint. If the p-value was less than 5%, then a comparison between MOA-728 12 mg QD and placebo for the second co-primary endpoint was performed. If that p-value was less than 5%, then a comparison between MOA-728 12 mg QOD and placebo for the second co-primary endpoint was performed. Two (2)-sided t-test was used for the second co-primary endpoint. A similar procedure was applied to the two key secondary endpoints, using 2-sided log-rank test or ANOVA (for the first and second key secondary endpoint, respectively). For the open label phase, only descriptive statistics are provided and no inferential analyses were performed. Missing efficacy data were imputed using the LOCF method as appropriate. Two (2) analyses were carried out based on observed data and the imputed data. The analyses based on the LOCF data were considered as the primary results.

Randomisation

A central computerised randomisation/enrolment (CORE II) system was used to assign randomisation numbers. Each subject's randomisation number was obtained by using the Web-based central randomisation system, which was available 24 hours a day. The randomisation number and the date on which the randomisation number was assigned were recorded on the CRF. Once subject numbers, package numbers, and randomisation numbers were assigned, they were not reassigned.

Blinding (masking)

Upon successful completion of the screening criteria and at baseline, subjects were randomly assigned to blinded doses of SC MOA-728 (12 mg) QD, MOA-728 (12 mg) QOD, or matching placebo in a 1:1:1 allocation ratio for the first 4 weeks (day 1 through day 28). For the double-blind phase, test article was packaged in individual vials containing MOA-728 (12 mg) or placebo. A qualified designee at the study site assigned, recorded, and dispensed boxes of double-blind test article to the subjects.

Statistical methods

The primary population analysed for efficacy analyses was the modified intent-to-treat (mITT) population, defined as subjects who were randomised and received at least one dose of double-blind test article. Analyses from the open-label phase were based on all subjects who received at least one dose of test article in the open-label phase.

The 2 co-primary efficacy endpoints are: (1) the proportion of subjects having a RFBM within 4 hours of the first dose administration, and (2) the percentage of active injections resulting in any RFBM within 4 hours during the double-blind phase.

Three (3) comparisons for the 2 co-primary endpoints were performed sequentially. A comparison between the combined MOA-728 groups (MOA-728 QD 12 mg and MOA-728 QOD 12 mg) and the placebo group was performed first using 2-sided Chi-square test for the first co-primary endpoint. If the p-value was less than 5%, then a comparison between MOA-728 12 mg QD and placebo for the second co-primary endpoint was performed. If that p-value was less than 5%, then a comparison between MOA-728 12 mg QOD and placebo for the second co-primary endpoint was performed. Two (2)-sided t-test was used for the second co-primary endpoint.

The 2 key secondary efficacy endpoints were: (1) time to the first RFBM after the first injection, censored at 24 hours or time of the second injection, whichever occurs first, and (2) change in weekly number of RFBMs from baseline to the double-blind phase.

Three (3) comparisons were performed for the 2 key secondary efficacy endpoints if all 3 comparisons for the 2 co-primary endpoints have p-values less than 0.05. A comparison (MOA-728 QD/QOD dose groups combined versus placebo) was performed using 2-sided log-rank test for the first key secondary efficacy endpoint. Comparisons between the MOA-728 QD dose group and placebo and between the MOA-728 QOD dose group and placebo were performed for the endpoint of change in weekly number of RFBMs from baseline during the double-blind phase, using an analysis of covariance (ANCOVA) model with treatment as a factor and baseline weekly RFBMs as a covariate. Hochberg Method was used to control the type 1 error at 0.05 level for these 3 comparisons.

The distribution of time to the first RFBM after the first injection, censored at 24 hours or time of the second injection, whichever occurs first, was estimated using the Kaplan-Meier method.

Results

Participant flow

A total of 1037 subjects were screened at 91 investigational sites in the United States and Canada for the study. 496 patients were finally randomised.

The following table shows the participant flow during the conduct of the study. 84.3% of the patient complete the double-blind phase, and shows the number and reasons for withdrawal of the 72 subjects which discontinued early.

Table. 6: Summary of reasons for conclusion of subjects participation during the double-blind phase: Safety population.

	Treatment			
Conclusion Status Reason[a]	MOA-728 12mg QD n=150	MOA-728 12mg QOD n=148	Placebo n=162	Total n=460
Total[b]	150 (100)	148 (100)	162 (100)	460 (100)
Completed	122 (81.3)	120 (81.1)	146 (90.1)	388 (84.3)
Double-Blind Phase Completed	122 (81.3)	120 (81.1)	146 (90.1)	388 (84.3)
Discontinued	28 (18.7)	28 (18.9)	16 (9.9)	72 (15.7)
Adverse Event	10 (6.7)	13 (8.8)	4 (2.5)	27 (5.9)
Failed to Return	6 (4.0)	4 (2.7)	1 (0.6)	11 (2.4)
Other	1 (0.7)	1 (0.7)	2 (1.2)	4 (0.9)
Protocol Violation	8 (5.3)	7 (4.7)	6 (3.7)	21 (4.6)
Subject Request	3 (2.0)	3 (2.0)	3 (1.9)	9 (2.0)

Abbreviations: QD = once daily; QOD = once every other day.

a. Total discontinued is the sum of individual reasons because they are mutually exclusive by subject.

b. Three (3) subjects did not complete the double-blind phase but entered the open-label phase of the study.

Source: /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3200K1 /3356/CPP4-DB - 23JAN09 14:46

Recruitment

Study Start Date: August 2007

Study Completion Date: December 2008

Conduct of the study

The protocol was amended twice after the original protocol was issued on 04 Jun 2007.

Amendment 1 (25 Sep 2007): Overall this amendment resulted in: increase in sample size, changes in primary endpoints and in several study procedures. The change in the primary endpoint to a co-primary endpoint led to a revised sample size calculation to ensure that the study was powered appropriately.

Amendment 2 (05 Aug 2008): Overall this amendment re-ordered the efficacy endpoints to be consistent with the endpoints in the pivotal phase 3 studies of MOA-728 for the treatment of OIC in patients with advanced illness who were receiving palliative care. In addition, minor and nonsubstantial changes were made to clarify a number of ambiguities in the protocol. Amendment 2 was implemented prior to the end of enrollment and did not result in a change in the required number of subjects or study procedures.

Baseline data

Demographic and baseline characteristics of subjects in the safety population during the double-blind phase are presented in Table 8-4. The results show that the 3 treatment groups were well balanced at study entry. The safety population during the double-blind phase consisted of more women (60.2%) than men (39.8%) with a mean age of 48.79 years. The majority of subjects were white (89.8%) and non-Hispanic/Latino (94.1%). As expected for a population with chronic pain and symptomatic OIC, most

of the subjects in the double-blind phase reported back pain (60.4%) as the primary pain condition at study entry. The mean duration of OIC among subjects in the safety population was 75.7 months: 76.4 months for subjects in the MOA-728 QD dose group, 76.1 months for subjects in the MOA-728 QOD dose group, and 74.5 months for subjects in the placebo group.

The median baseline dose of opioid medication was 160.0 mg/day in the overall safety population, which is expressed as oral morphine equivalents.

Table 8-4: Summary of Demographic and Baseline Characteristics of Subjects in the Double-Blind Phase: Safety Population

Characteristic	MOA-728 12mg QD (n =	MOA-728 12mg QOD (n = 148)	Placebo (n = 162)	Total (n =
Age (Years), N				
N	150	148	162	460
Mean	47.99	48.64	49.69	48.79
Standard Deviation	10.74	11.05	10.77	10.85
Minimum	24.00	23.00	25.00	23.00
Maximum	78.00	73.00	83.00	83.00
Median	48.00	48.50	49.00	49.00
Sex, N (%)				
Male	57 (38.0)	63 (42.6)	63 (38.9)	183 (39.8)
Female	93 (62.0)	85 (57.4)	99 (61.1)	277 (60.2)
Race, N (%)				
Asian	2 (1.3)	1 (0.7)	1 (0.6)	4 (0.9)
Black or African American	7 (4.7)	10 (6.8)	15 (9.3)	32 (7.0)
White	139 (92.7)	133 (89.9)	141 (87.0)	413 (89.8)
Other	2 (1.3)	4 (2.7)	5 (3.1)	11 (2.4)
Ethnic Origin, N (%)				
Hispanic or Latino	10 (6.7)	8 (5.4)	9 (5.6)	27 (5.9)
Non-Hispanic and Non-Latino	140 (93.3)	139 (94.6)	153 (94.4)	432 (94.1)
Missing	0	1	0	1
Primary Pain Condition, N (%)				
Back pain	96 (64.0)	83 (56.1)	99 (61.1)	278 (60.4)
Cervical/Neck pain	6 (4.0)	10 (6.8)	5 (3.1)	21 (4.6)
Complex regional pain syndrome	3 (2.0)	0	2 (1.2)	5 (1.1)
Fibromyalgia	13 (8.7)	9 (6.1)	8 (4.9)	30 (6.5)
Low extremity/hip pain	4 (2.7)	10 (6.8)	9 (5.6)	23 (5.0)
Migraines/headaches	2 (1.3)	1 (0.7)	1 (0.6)	4 (0.9)
Neuropathic	4 (2.7)	11 (7.4)	6 (3.7)	21 (4.6)
Osteroarthritis	12 (8.0)	11 (7.4)	13 (8.0)	36 (7.8)
Others	4 (2.7)	8 (5.4)	9 (5.6)	21 (4.6)
Pelvic pain	1 (0.7)	0	4 (2.5)	5 (1.1)
Rheumatoid arthritis	2 (1.3)	3 (2.0)	2 (1.2)	7 (1.5)
Trigeminal neuralgia	1 (0.7)	0	1 (0.6)	2 (0.4)
Upper extremity/shoulder pain	2 (1.3)	2 (1.4)	3 (1.9)	7 (1.5)
Baseline Morphine Equivalent Dose (mg), N				
N	150	148	162	460
Mean	214.39	225.20	225.02	221.61
Standard Deviation	156.58	205.07	215.63	194.32
Minimum	45.45	7.15	13.57	7.15
Maximum	831.16	1334.29	1286.47	1334.29
Median	161.00	154.76	160.81	160.00
Duration of Opioid Induced Constipation (months), N				
N	150	148	162	460
Mean	76.44	76.10	74.54	75.66
Standard Deviation	60.35	74.11	67.32	67.32

Characteristic	MOA-728 12mg QD (n =	MOA-728 12mg QOD (n = 148)	Placebo (n = 162)	Total (n =
Minimum	2.82	2.30	2.00	2.00
Maximum	322.46	453.94	445.09	453.94
Median	60.44	53.83	57.92	58.11
Baseline Height (cm), N				
N	150	148	162	460
Mean	169.51	171.13	169.80	170.14
Standard Deviation	9.22	11.24	10.53	10.37
Minimum	147.30	147.00	144.80	144.80
Maximum	189.20	205.70	193.00	205.70
Median	168.00	170.20	170.20	170.20
Baseline Weight (kg), N				
N	150	148	162	460
Mean	87.48	85.09	87.16	86.60
Standard Deviation	25.03	21.86	26.28	24.49
Minimum	40.40	43.50	44.90	40.40
Maximum	170.60	163.30	215.20	215.20
Median	84.55	83.40	83.95	83.95
Baseline BMI (kg/m2), N				
N	150	148	162	460
Mean	30.28	28.87	30.07	29.76
Standard Deviation	7.77	6.1	8.02	7.3
Minimum	16.80	15.70	15.70	15.70
Maximum	56.50	54.70	66.20	66.20
Median	28.90	27.95	28.50	28.55

Abbreviations: QD = once daily; QOD = once every other day.

Source: /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3200K1 /3356/DEMO4-DB - 22MAY09 13:46 and DURA4-DB - 08APR09 17:05

Demographic and baseline characteristics of the subjects in the safety population during the open-label phase were consistent with those in the double-blind phase

Numbers analysed

A total of 460 subjects were randomised and received treatment in the double-blind phase of the study including: 150 subjects in the MOA-728 QD treatment group, 148 in the MOA-728 QOD treatment group, and 162 in the placebo treatment group. Efficacy analyses were performed on all 460 subjects in the mITT population.

A total of 364 subjects received at least 1 dose of open-label treatment. The majority of subjects with OIC who entered the open-label phase had chronic back pain (60.2%) as the primary pain condition requiring symptomatic opioid-therapy.

Protocol violation was the reason for not completing the study for 21 (4.6%) subjects in the double-blind and 21 (5.8%) in the open-label phases. The most common reasons for protocol violations resulting in discontinuation were noncompliance of reporting diary information through IVRS, noncompliance with laxative use, and subjects who entered the study and did not meet baseline inclusion/exclusion criteria.

Outcomes and estimation

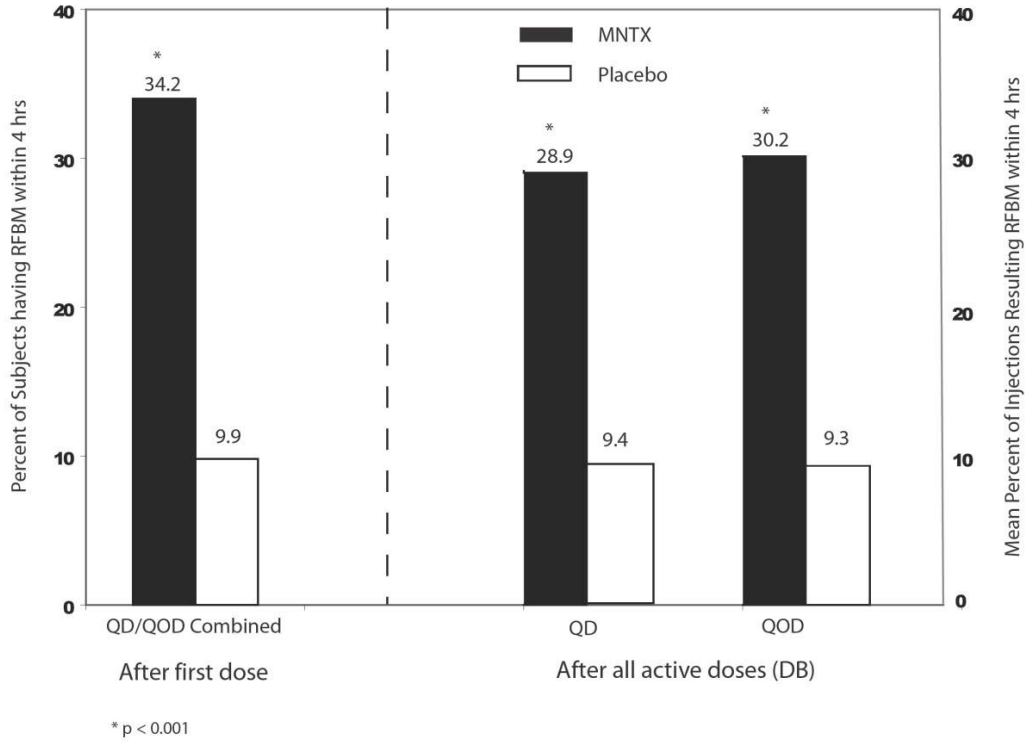
Primary efficacy endpoints

The proportion of patients with an RFBM within four hours after the first dose (the first of two co-primary endpoints) was significantly higher in the MNTX-treated patients than in the placebo patients (34% versus 10%, respectively; $p<0.001$).

The percentage of active injections resulting in an RFBM within four hours after dosing through the four-week double-blind period (the second co-primary endpoint) was calculated using all the injections from the MNTX QD group but only the active injections from the MNTX QOD group. Results for this endpoint were calculated using daily injections for MNTX versus daily injections for placebo for the MNTX QD group; however, for the MNTX QOD group, the QOD injections of active drug were only compared against the corresponding QOD injections of placebo drug.

The calculated percentage was 29% and 30% for the MNTX QD and MNTX QOD dose regimens, respectively, compared with 9% for each corresponding placebo regimen ($p<0.001$ for each comparison) during the four-week, double-blind period, as shown in Figure 1.

Figure 1: RFBM response within four hours after the first dose and within four hours after all active doses of the four-week (double-blind) period: mITT population (Study 3356)



Reference: Study 3200K1-3356-WW CSR, Figure 9-1
Note: P-values are based on a two-sided Chi-square test for the responses following the first dose and two-sided t-tests for the responses following all double-blind doses.
Abbreviations: DB=double blind; mITT=modified intent-to-treat; MNTX=methylnaltrexone; QD=once daily; QOD=once every other day; RFBM=rescue-free bowel movement.

Secondary efficacy endpoints

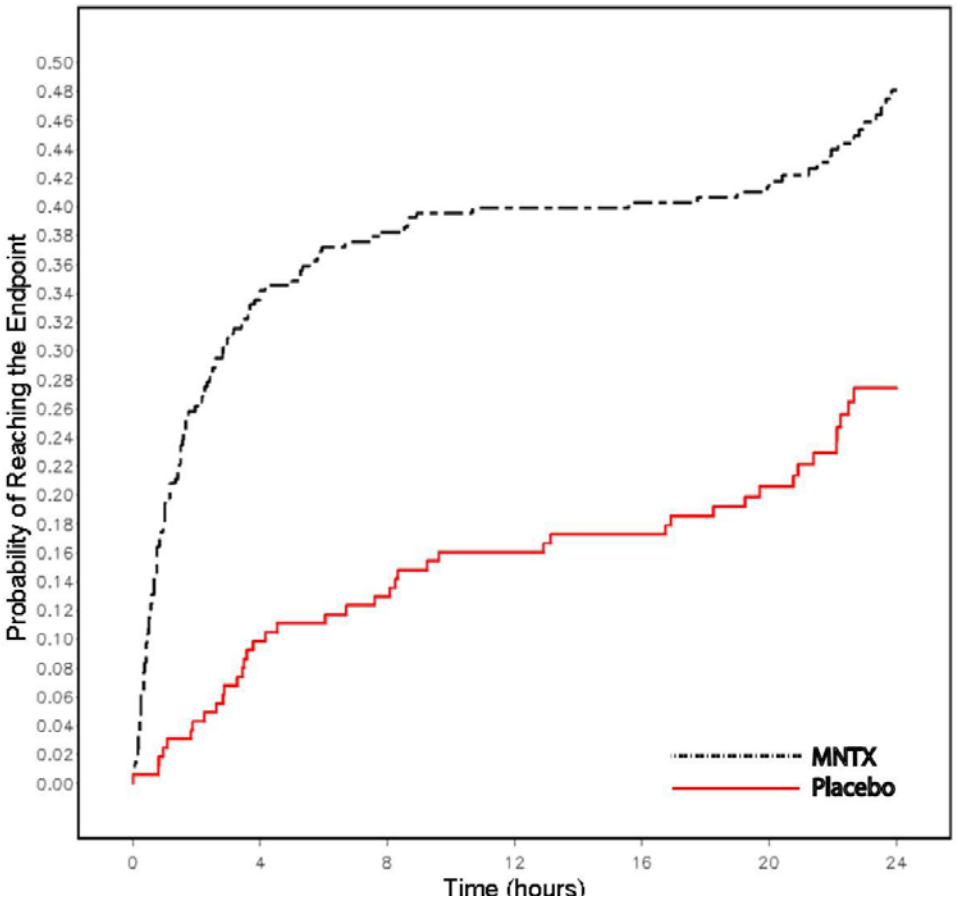
Time to first RFBM

Figure 2 provides a graphic display of the Kaplan-Meier analysis for time to the first RFBM within 24 hours after the first dose of treatment. The difference in time to the first RFBM following first dose is statistically significant based on the log-rank test ($p<0.001$) for the combined MNTX treatment group versus placebo. The separation between the MNTX-treated patients and the placebo group occurs quickly after dose administration and increases up to four hours after dosing point (Figure 2). Little additional differentiation between MNTX and placebo treatment occurs after four hours, but the difference between the groups seen up to four hours after dosing persisted throughout the 24-hour time period. Among

patients who had an RFBM within four hours after the first dose, the median time to an RFBM was 0.8 hours in the MNTX- treated patients and 2.4 hours in the placebo group.

The median times to the first RFBM after the first dose of treatment were 22.1 hours in the MNTX QD group, 28.1 hours in the MNTX QOD group, and 48.9 hours in the placebo group ($p<0.001$ for each comparison).

Figure 2: Kaplan-Meier plot of time to the first RFBM following the first dose: mITT population (Study 3356)



Reference: Study 3200K1-3356-WW CSR, Figure 9-2
Note: Censored at 24 hours or at time of the second dose
Abbreviations: mITT=modified intent-to-treat; MNTX = methylnaltrexone; RFBM=rescue-free bowel movement.

Change in weekly number of RFBMs

Increase from baseline in average weekly RFBMs, the second key secondary endpoint, was significantly higher in the MNTX QD and QOD groups compared with the placebo group for the four-week period ($p<0.001$ and $p=0.011$, respectively).

Table 29: ANCOVA results for change in weekly number of RFBMs by treatment group during the four-week (double-blind) period: mITT population with last observation carried forward data (Study 3356)

					Difference in Adjusted Change vs. Placebo	
Treatment	**N**	**Raw Mean (SD)**	**Raw Mean Change (SD)**	**Adjusted Mean Change (SE)**	**Mean (95% CI)**	**p-value[a]**
MNTX 12 mg QD	150	4.1 (2.9)	3.1 (2.9)	3.1 (0.2)	1.6 (1.1, 2.1)	<0.001
MNTX 12 mg QOD	148	3.1 (2.1)	2.2 (2.0)	2.1 (0.2)	0.7 (0.2, 1.2)	0.011
Placebo	162	2.6 (1.9)	1.4 (1.8)	1.5 (0.2)		

Reference: Study 3200K1-3356-WW CSR, Table 9-7
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; mITT=modified intent-to-treat; QD=once daily; QOD=once every other day; RFBM=rescue-free bowel movement; SD=standard deviation; SE=standard error.
[a] P-value versus placebo group was based on ANCOVA Model change=baseline+treatment.

The results for some of the additional endpoints are given in the following tables:

Table 8: ANCOVA results of average straining scale of RFBMs by treatment group: mITT with LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo	
DAI	**Treatment**	**N**	**Mean(Sd)**	**Mean(Sd)**	**Mean(SE)**	**Mean (95% CI)**	**P-value[a]**
DB Treatment	MOA-728 12 mg QD	150	1.7(1.0)	-1.2(1.1)	-1.1(0.1)	-0.3(-0.5,-0.1)	0.008
	MOA-728 12 mg QOD	148	1.7(1.0)	-1.0(1.2)	-1.1(0.1)	-0.2(-0.5,-0.0)	0.015
	Placebo	162	1.9(0.9)	-0.7(1.0)	-0.8(0.1)		

Table 9: ANCOVA of average of percentage of RFBMS with BSFS 6 or 7 (diarrhoea or watery: mITT with LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo	
DAI	**Treatment**	**N**	**Mean(Sd)**	**Mean(Sd)**	**Mean(SE)**	**Mean (95% CI)**	**P-value[a]**
DB Treatment	MOA-728 12 mg QD	150	15.7(23.6)	12.8(25.9)	11.7(1.8)	5.6(0.8,10.4)	0.023
	MOA-728 12 mg QOD	148	13.9(21.7)	8.1(23.5)	8.8(1.8)	2.8(-2.0,7.6)	0.258
	Placebo	162	10.9(21.8)	5.7(23.1)	6.1(1.7)		

Table 10: ANCOVA results of average BSFS of RFBMs by treatment group: mITT with LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo	
DAI	**Treatment**	**N**	**Mean(Sd)**	**Mean(Sd)**	**Mean(SE)**	**Mean (95% CI)**	**P-value[a]**
DB Treatment	MOA-728 12 mg QD	150	3.3(1.4)	1.4(1.6)	1.4(0.1)	0.5(0.2,0.7)	0.002
	MOA-728 12 mg QOD	148	3.1(1.4)	1.1(1.5)	1.2(0.1)	0.2(-0.1,0.5)	0.119
	Placebo	162	2.9(1.4)	0.9(1.4)	0.9(0.1)		

Table 11: ANCOVA results of average percentage of RFBMs with a sensation of complete evacuation by treatment group: mITT with LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo	
DAI	Treatment	N	Mean(Sd)	Mean(Sd)	Mean(SE)	Mean (95% CI)	P-value[a]
DB Treatment	MOA-728 12 mg QD	150	45.1(34.8)	29.3(37.7)	27.4(2.6)	7.6(0.4,14.7)	0.038
	MOA-728 12 mg QOD	148	42.9(34.1)	24.6(37.6)	24.2(2.6)	4.3(-2.8,11.5)	0.237
	Placebo	162	40.5(35.4)	17.8(35.6)	19.9(2.5)		

Table 12: ANCOVA results of average percentage of RFBMs with BSFS 3 or 4 (=normal consistency): mITT with LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo	
DAI	Treatment	N	Mean(Sd)	Mean(Sd)	Mean(SE)	Mean (95% CI)	P-value[a]
DB Treatment	MOA-728 12 mg QD	150	33.2(28.6)	18.9(34.7)	18.7(2.4)	1.1(-5.4,7.7)	0.731
	MOA-728 12 mg QOD	148	33.6(31.1)	17.1(37.1)	18.5(2.4)	0.9(-5.6,7.5)	0.779
	Placebo	162	31.8(31.2)	18.6(35.9)	17.6(2.3)		

Table 13: ANCOVA results of average percentage of RFBMs with straining scale of 0 or 1 (no or mild) by treatment group: mITT with LOCF

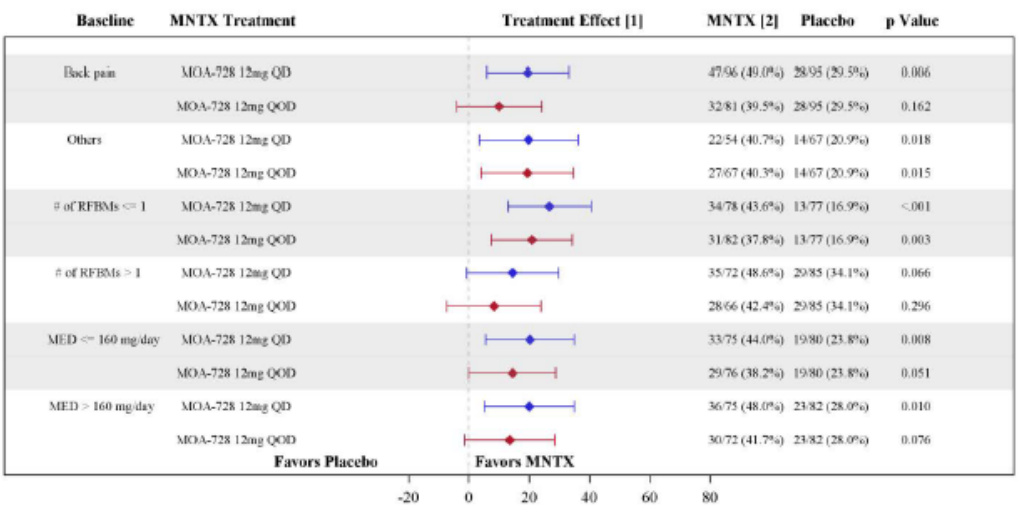
			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo	
DAI	Treatment	N	Mean(Sd)	Mean(Sd)	Mean(SE)	Mean (95% CI)	P-value[a]
DB Treatment	MOA-728 12 mg QD	150	44.4(36.7)	33.9(42.4)	31.5(2.8)	7.0(-0.6,14.5)	0.071
	MOA-728 12 mg QOD	148	46.6(35.0)	28.2(39.7)	31.1(2.8)	6.6(-1.0,14.2)	0.087
	Placebo	162	38.3(34.0)	24.9(35.6)	24.5(2.7)		

During the open-label phase of the study, patients were allowed to reduce the number of injections, and did so by injecting between 4 and 5 doses per week consistent over all former treatment groups. The evaluation of the clinical endpoints, consisting of the mean percentage of injections resulting in any RFBM within 4 hours, the mean number of RFBM per week and the number of CRFBMs per week showed a constant difference compared to baseline, without strong changes over time.

Ancillary analyses

A consistent efficacy was shown across subpopulations: This is shown in the following graph, which includes the following subgroups: Underlying pain condition, baseline number of RFBMs per week, and baseline opioid dose.

Figure 17: **Subjects Achieving ≥ 3 RFBMs per Week and an Increase of at Least 1 from Baseline for 3 out of 4 Weeks During the Double-Blind Phase of Study 3356 (Worst Case Method)**



Summary of main study

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

Table 1. Summary of Efficacy for trial 3200K1-3356-WW

Title: A Multicenter, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study Of Subcutaneous Moa-728 For The Treatment Of Opioid-Induced Constipation In Subjects With Chronic Non-Malignant Pain		
Study identifier	3200K1-3356-WW	
Design	A Phase 3, multicenter, double-blind, randomised, parallel-group, placebo-controlled followed by an open-label phase study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	4 weeks Not applicable 8 weeks open label
Hypothesis	Superiority	
Treatments groups	12 mg MOA-728 (QD)	**Treatment**: once per day (QD) SC administration **Duration:** up to 84 days, **Number randomised**: 150
	12 mg MOA-728 (QOD)	**Treatment**: once every other day (QOD) SC administration **Duration:** up to 84 days, **Number randomised**: 148

	Placebo		**Treatment**: once per day (QD) SC administration **Duration:** up to 84 days, **Number randomised**: 162
Endpoints and definitions	Co-Primary endpoint		The proportion of subjects having an RFBM within 4 hours of the first dose administration
	Co-Primary endpoint		The percentage of active injections resulting in any RFBM within 4 hours during the double-blind phase
	Key Secondary endpoint		Time to the first RFBM after the first injection, censored at 24 hours or time of the second injection, whichever occurs first
	Key Secondary endpoint		Change in weekly number of RFBMs from baseline to the double-blind phase
Database lock			

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	modified Intent to Treat Subjects who were randomised and received at least one dose of double-blind test article in the double blind phase.			
Descriptive statistics and estimate variability	Treatment group	MOA-728 (QD)	MOA-728 (QOD)	Placebo
	Number of subject	150	148	162
	Having an RFBM within 4 hours of the first dose	50 (33.3%)	52 (35.1%)	16 (9.95)
	(95% CI)	(14.6, 32.3)	(16.3, 34.2)	-
	Percentage of active injections resulting in any RFBM within 4 hours	28.9 (mean)	30.2 (mean)	9.3 (mean)
	(95% CI)	(15.1, 24.1)	(16.1, 25.7)	-

	Time to the first RFBM after the first injection, censored at 24 hours or time of the second injection (<statistic>)	74 (49.3%)	63 (42.6%)	41 (25.3%)
	p-value	<0.001	<0.001	
	Change in weekly number of RFBMs from baseline to the double-blind phase	3.1	2.2	1.4
	(95% CI)	<0.001	0.011	-

Effect estimate per comparison	Having an RFBM within 4 hours of the first dose	Comparison groups	MOA-728 QD/QOD vs placebo
		%	34.2%
		95% CI	17.3, 31.4%
		P-value	<0.001
	Percentage of active injections resulting in any RFBM within 4 hours	Comparison groups	MOA-728 QD vs placebo
		Difference	19.5
		95% CI	15.1, 24.0
		P-value	<0.001
	Percentage of active injections resulting in any RFBM within 4 hours	Comparison groups	MOA-728 QD vs placebo
		Difference	20.9
		95% CI	16.1, 25.7
		P-value	<0.001
Notes			
Analysis description	**Co-primary Analysis & Secondary analysis**		
	See above.		

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

No pooled analysis is presented due to the fact that only one pivotal study has been conducted.

Clinical studies in special populations

No studies in special populations were presented which is acceptable.

Supportive studies

Study 3358 was a multi-centre, open-label, phase 3 study in patients with non-cancer pain and OIC conducted at 120 investigational sites in the USA, Canada, Australia, Spain, Korea, and Colombia. The study was conducted between December 2008 and September 2010.

The primary objective of the study was to evaluate the long-term safety and tolerability of the SC MNTX 12 mg administration in this patient population. The secondary objective of the study was to assess the long-term efficacy of the SC MNTX administration.

The study consisted of a 2 week screening period, a 48-week open-label treatment period, and a 2-week post-treatment follow-up. The dosing during the 48-week period was 12 mg MNTX SC administered daily, which could be adjusted to an as needed basis with a minimum does of 1 per week.

In- and exclusion criteria were resembling those of the double-blind study. The efficacy measurements included the following: The percentage of injections resulting in BM within 4 hours, the average of BM Bristol Stool Scale, the average of BM Straining Scale and the average percentage of BMs with a sensation of complete evacuation.

A total of 1673 subjects were screened, of which 1040 were assigned to treatment, and 1034 were randomised. Of these, 477 completed the whole duration of the trial. Of the 54% discontinuations of the study, 15% discontinued due to AEs, 12.7% due to subject request, and 9.3% “failed to return”. 8.2% had protocol violations, 4.4% unsatisfactory efficacy response, and 2.8% other reasons. 4 subjects (0.4%) died during the trial.

The mean percentage of injections resulting in BMs within 4 hours was 34% without relevant fluctuation across the duration of the study, the weekly BM rate was a mean of 3.9, the percentage of BMs with a sense of complete evacuation was about 55%, and the average BFSF of BMs was 3.6, again without relevant fluctuation in all these parameters.

Study 3201 was a phase 3, double-blind, placebo-controlled, parallel-group study, evaluated the safety and efficacy of an oral MNTX tablet formulation versus placebo in subjects with chronic nonmalignant pain with OIC. Subjects were randomly assigned to receive oral MNTX 150, 300, or 450 mg once daily (QD), or placebo QD in a 1:1:1:1 allocation ratio. Subjects took study drug QD during the first 28 days; dosing was as needed during the remaining 56 days of the 12 week treatment period. MNTX was supplied as 150 mg tablets; all patients took 3 tablets per day of study drug and/or placebo to maintain the blind. Study drug was ingested first thing in the morning on an empty stomach (prior to breakfast). A total of 803 subjects with OIC and chronic, non-cancer pain were enrolled, randomised to 1 of 4 treatment groups, and received ≥ 1 dose of study medication (201, 201, and 200 subjects in the 150, 300, and 450 mg/day groups, respectively, and 201 in the placebo group).

The primary endpoint for study 3201 was the average percentage of RFBMs per subject within 4 hours of all doses during the first 4 weeks of dosing. This endpoint was the same as the second of the co-primary endpoints in the pivotal study of SC MNTX (3356) in patients with OIC associated with noncancer pain.

For the primary endpoint, highly statistically significant improvements were observed for the MNTX 300 and 450 mg/day groups compared to the placebo group in the ITT population ($p = 0.0016$ and $p < 0.0001$, respectively). Dose-dependent increases in primary endpoint responses were observed across increasing MNTX dose levels ($p < 0.0001$ for linear dose response; 18.2%, 21.1%, 24.6%, and 27.4% of subjects in the placebo, 150, 300, and 450 mg/day groups, respectively, had RFBMs within 4 hours of all doses during Weeks 1 through 4).

Comparison of an equivalent endpoint (average percentage of RFBMs per subject within 4 hours of dosing during the treatment period) between oral dosing in study 3201 (primary endpoint) and SC dosing in

study 3356 (second of the co-primary endpoints) indicated consistent, statistically significant efficacy of MNTX across studies (3356 results – see section 3.2.1.2; 3201 results – presented above).

Results for the key secondary efficacy endpoints are the following:

- There were significant greater increases from baseline in the weekly number of RFBMs over the first four weeks of dosing in the MNTX 300 and 450 mg/day groups compared with the placebo group ($p = 0.0109$ and $p = 0.0083$, respectively, first key secondary endpoint). The LS mean difference versus placebo in the changes from baseline during Weeks 1 – 4 were 0.58 and 0.60 for the 300 and 450 mg/day groups, respectively.

- The proportion of responders during Weeks 1 through 4 were significantly greater in the MNTX 300 and 450 mg/day groups compared with the placebo group ($p = 0.0415$ and 0.0056, respectively) in the last-observation-carried-forward (LOCF) analysis (second key secondary endpoint). The percentages of responders were 47.8% and 50.5% in the MNTX 300 and 450 mg/day groups, respectively, compared with 37.3% in the placebo group. A responder was defined as a subject who had ≥ 3 RFBMs/week, with an increase of ≥ 1 RFBM/week over baseline, for ≥ 3 of the first 4 weeks of treatment. Additional secondary efficacy endpoints results include the following:

Time to first RFBM: Subjects in all MNTX treatment groups had significantly shorter times to first RFBM compared to placebo ($p = 0.0160$ for the 150 mg/day group and $p < 0.0001$ for each of the 300 and 450 mg/day groups). Also, significantly higher proportions of MNTX-treated subjects had RFBMs within 4 hours ($p < 0.0001$ for each of the 300 and 450 mg/day doses) and within 24 hours ($p = 0.0193$, $p = 0.0002$, and $p < 0.0001$ for the 150, 300, and 450 mg/day doses, respectively) following the first dose of study drug when compared with placebo-treated subjects.

Durable efficacy: Efficacy of MNTX, with respect to the average percentage of RFBMs within four hours of dosing (primary efficacy variable), was durable over the course of the 12 week treatment period.

- In MNTX to placebo comparisons at each week, there were significant ($p < 0.05$) treatment differences in primary endpoint responses compared to placebo at most time points for the 300 and 450 mg/day groups from Week 1 up to Week 12 of the study.

- In MNTX to placebo comparisons over the entire 3 month period, there were significant improvements in primary endpoint responses in the 300 mg/day and 450 mg/day groups.

The proportions of primary endpoint responses over the entire treatment period was 25% and 28% for the MNTX 300 and 450 mg/day groups, respectively, and 19% for the placebo group ($p = 0.0020$ and $p < 0.0001$, respectively).

- A durable MNTX treatment effect was observed in the proportions of overall responders during the 12 week treatment period; there were significantly greater proportions of responders for ≥ 9 of 12 weeks in the 450 mg/day MNTX group versus placebo. A total of 41%, 40%, and 49% of subjects were overall responders for the MNTX 150, 300, and 450 mg/day groups, respectively ($p = 0.0006$ for the 450 mg/day group versus placebo). Responders were defined as subjects with ≥ 3 RFBMs per week and an increase of ≥ 1 from baseline (second key secondary efficacy variable), and overall responders were responders for ≥ 9 of 12 weeks (ie, ≥ 75% of the weeks).

The effectiveness of oral MNTX led to significantly less days requiring rescue laxatives in the 450 mg/day group when compared to placebo in this study. The percentage of total study days requiring rescue laxative therapy were 6.20% in the placebo group and 4.27% in the MNTX 450 mg/day group ($p = 0.0253$).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH has presented a phase II study randomised, placebo-controlled study of short-term use of MNTX (study 2101) conducted in patients with OIC after orthopaedic surgery. A treatment duration of at least seven days was expected. The endpoints used for efficacy evaluation were the induction of prompt laxation after certain time-points, and the time to laxation events, indicating pharmacodynamic activity. From this study, it can be concluded that the compound does develop a relevant pharmacodynamic activity and might be suitable for longer-term treatment of patients with OIC.

The pivotal phase III study (study 3356) in support of the proposed treatment of the new patient population of patients with non-malignant pain suffering from opioid-induced constipation included a study population receiving opioids and suffering from constipation induced by this medication for longer periods of time (at least one month at screening). The study was designed as a placebo-controlled study with four weeks duration, comparing 12 mg SC MNTX OD, and 12 mg SC QOD with placebo in a double blind manner for four weeks. An additional open-label treatment phase of 8 weeks was also included. The overall study design with a run-in period for the evaluation of the fulfilment of the inclusion criteria, and the randomisation, and double-blind treatment phase is considered acceptable. The 4 week treatment period (in double-blind fashion) can be considered sufficient in this setting taking into consideration that Relistor is already authorised in the advanced illness population (mostly cancer patients).

The treatment groups of the double-blind phase of the trial were reasonably balanced. The mean age was 49 years, and the majority of the patients (60.2%) were female. The duration of opioid induced constipation was around 75 months in the mean, with no relevant deviations between the groups. Concomitant treatment with “usual laxatives” was to be discontinued before inclusion in the study which is also reflected in the non-cancer patients in the SmPC (section 4.2).

The majority of patients (88%) in Study 3356 were constipated at study entry while taking one or more laxatives. The “validation” of the “insufficient response to laxatives” was only done by history taking, which is not defining a clear “insufficient response”-population but most likely include a relatively heterogeneous population comprising partial responders to “null-responders”. During the run-in period of study 3356, no “background medication” was given (in order to ascertain the insufficient response to laxatives) but only rescue medication could be used. It is therefore considered that the included patient population do only slightly differ from the clear second line indication and that efficacy was assessed in this setting. To address this concern the MAH agreed to amend the indication to second line (when response to usual laxative therapy has not been sufficient) in accordance with the already existing indication in the advanced illness population. Since the pharmacodynamic action of a μ-receptor antagonist does not depend on the reason why the opioid is given, the indication statement was summarised to the treatment of OIC when response to usual laxative therapy has not been sufficient in adult patients. The posology remains separated for the different patient populations due to the potential differences regarding efficacy and safety, the doses used in the underlying studies, and the different background medication.

The number of discontinuations was high during the double-blind, as well as during the open-label phase of the study, with more than 30% of the patients discontinuing the study within 3 months. Furthermore – during the double-blind phase – the number of drop-outs has been considerably higher in the active treatment groups compared to placebo. To give assurance on external validity of the study as a selected patient population could have introduced bias, especially towards the end of the evaluation period, and to account for a differential drop-out additional sensitivity analyses were presented showing a minor influence of the differential drop-out on the overall outcome of the trial.

The company has additionally conducted a long-term open-label study with one year duration. This study evaluated efficacy as a secondary objective. Notwithstanding the discontinuation rate, which was high across the whole duration of the trial and might have led to a "positive" selection of patients with good treatment response and without tolerability problems, the results indicated relevant changes from baseline which were sustained during the whole treatment period.

The company had chosen in the development program to use mainly primary and secondary endpoints expressing an immediate clinical activity (within certain time-points in close relation to study drug administration). It is considered that induction of laxation within an early point of time after administration needs to relate well to the increase in overall frequency of laxation, the (change of the) consistency of the stool, and, after all, the complaints associated with the bowel movements, such as a feeling of completeness of evaluation, straining, and other pain- and non-pain related symptoms to be of clinical relevance.

Efficacy data and additional analyses

The evaluation of the pivotal study has shown a high numerical and statistically significant superiority of the active treatment groups over placebo in the two co-primary and the key secondary endpoints. These effects appear to be consistent across the whole double-blind treatment period. These results are supported by the evaluation of the PAC-SYM, and the PAC-QOL, both general questionnaires for the evaluation of gastrointestinal symptoms in constipation and the related quality of life.

Whereas primary and secondary endpoints expressing an immediate clinical activity (within an early point of time after administration) are not considered to measure a clinical meaningful effect they were complemented by further secondary endpoints and analysis expressing more targeted clinical relevance.

The proportion of patients with ≥3 RFBMs per week during the 4-week double-blind phase was 59% of the patients in the group receiving daily methylnaltrexone 12 mg ($p<0.001$ vs. placebo), in 61% of those receiving it every other day ($p<0.001$ vs. placebo), and in 38% of the placebo treated patients. Supplementary analysis evaluated the percentage of patients achieving ≥3 complete RFBMs per week and an increase of ≥1 complete RFBM per week in at least 3 of the 4 treatment weeks. This was achieved in 28.7% of the patients in the group receiving daily methylnaltrexone 12 mg ($p<0.001$ vs. placebo), in 14.9% of those receiving it every other day ($p=0.012$ vs. placebo), and in 6.2% of the placebo treated patients.

Whereas an ideal measure of looking into clinical efficacy is regarded to be an endpoint combining increase in overall frequency of laxation, the (change of the) consistency of the stool, and, after all, the complaints associated with the bowel movements, such as a feeling of completeness of evaluation, straining, and other pain- and non-pain related symptoms, setting certain thresholds for the fulfilment of a treatment response the MAH was able to show consistent effects in most of these other more "relevant" domains of efficacy,

In the lower dose group the numerical values and rates of responders were reduced compared with the high dose group (and the differences to placebo were reduced). For some of these endpoints, the lower dose did not reach statistical significance pointing to a diminished effect. Considering the recommended posology (as needed, given as at least 4 doses weekly) this does not pose a concern.

Consistency of results across different population subgroups was shown for different underlying pain condition, baseline severity of constipation, and baseline opioid dose. Consistency was also shown for age, gender, race, and body weight but to a lesser extent.

The open-label phase of the study has shown consistency with regard to the results achieved in the primary and secondary endpoints used in the double-blind phase and a clear tendency for a reduced effect over time could not be anticipated. To draw reliable conclusions from an open-label extension phase on the long term persistence of efficacy is difficult but it is taken into consideration that the results of the open-label extension and the long-term safety study demonstrate overall consistent effects over time - not showing any reduction in effects in the long-term. Moreover, the applicant presented in the course of the procedure data from a 3-months study in OIC with an oral formulation of MNTX (dose: 450 mg), which did show consistent superiority over placebo for the duration of three months. Considering the overall pharmacology of the substance, it can be assumed that the efficacy shown in the 4-weeks trial persists for longer treatment periods.

2.4.4. Conclusions on the clinical efficacy

Clinical relevance and durability of the effect in the studied patient population has been shown to a sufficient extend. Despite somewhat diminished efficacy in the lower dose group the recommended posology given as at least 4 doses weekly is acceptable as it can be increased to up to 7 doses weekly if needed.

Considering that the patients included in the pivotal trial comprising a population of partial responders to “null-responders” and efficacy was assessed in this setting the indication statement was adapted to reflect a second line treatment.

Since the pharmacodynamic action of a μ-receptor antagonist does not depend on the reason why the opioid is given and consistency of results was shown across different population subgroups, the indication statement was summarised to the treatment of OIC when response to usual laxative therapy has not been sufficient in adult patients.

However, due to the potential differences with regard to efficacy and safety, the doses used in the underlying studies, and the different background medication, a simple single posology could not be introduced. This has still to differentiate between the overall pain population and the palliative care population studied for the initial licensing.

2.5. Clinical safety

Introduction

The known safety profile of the compound can be regarded to be relatively “benign”, acting primarily on the gastrointestinal tract. The most frequent undesirable effects are diarrhoea, abdominal pain, flatulence, nausea and vomiting. In addition, frequently observed events include dizziness, and injection site reactions.

Patient exposure

The patient exposure for the SC double-blind pool is described in the following tables:

Table 14: Extent of exposure SC double-blind pool (discontinuations):

Parameter	Double Blind Period All Combined MNTX (N=316) n (%)	Open Label Period All Combined MNTX (N=1398) n (%)
Final Patient Status, n (%)		
Patients who completed study	257 (81.3)	779 (55.7)
Patients who withdrew	59 (18.7)	619 (44.3)
Reason for Early Termination, n (%)		
AE	25 (7.9)	168 (12.0)
Protocol violation	15 (4.7)	106 (7.6)
Lack of efficacy	0	52 (3.7)
Lost to follow-up	10 (3.2)	105 (7.5)
Withdrawal by patient	7 (2.2)	142 (10.2)
Death	0	4 (0.3)
Investigator's request	0	8 (0.6)
Other	2 (0.6)	46 (3.3)

Table 15: Extent of exposure SC double-blind pool (duration):

Parameter	MNTX 12 mg QD (N=168) n (%)	MNTX 12 mg QOD (N=148) n (%)	MNTX 12 mg QD/QOD (N=316) n (%)
Duration of Drug Exposure (days)			
Mean (SD)	23.35 (9.864)	24.67 (8.230)	23.97 (9.145)
Min, Max	1.0, 32.0	1.0, 31.0	1.0, 32.0
Duration of Drug Exposure in Time Intervals, n (%)			
≤1 day	5 (3.0)	10 (6.8)	15 (4.7)
>1 day - 7 days	25 (14.9)	5 (3.4)	30 (9.5)
>7 day - 14 days	4 (2.4)	4 (2.7)	8 (2.5)
>14 day - 28 days	63 (37.5)	68 (45.9)	131 (41.5)
>4 weeks (>28 days)	71 (42.3)	61 (41.2)	132 (41.8)
Duration of Study Exposure (days)			
Mean (SD)	75.39 (36.373)	80.26 (31.021)	77.67 (34.006)
Min, Max	1.0, 161.0	2.0, 123.0	1.0, 161.0
Total Number of Doses Received			
Mean (SD)	23.10 (9.839)	12.66 (4.128)	18.21 (9.301)
Min, Max	1.0, 32.0	1.0, 16.0	1.0, 32.0

Adverse events

The overall number of adverse events (AEs), with the evaluation of emergence from treatment, relatedness, severity, being life-threatening, being serious, serious and related, and leading to discontinuation or death are shown in the following tables showing the double-blind and the SC only pools separately:

Table 16: Overview of adverse events: SC double-blind pool:

Parameter	MNTX 12 mg QD (N=168) n (%)	MNTX 12 mg QOD (N=148) n (%)	MNTX 12 mg QD/QOD (N=316) n (%)	Placebo (N=177) n (%)	Overall (N=493) n (%)
Number (%) of Patients with					
At least one AE, n (%)	90 (53.6)	69 (46.6)	159 (50.3)	67 (37.9)	226 (45.8)
At least one TEAE, n (%)	82 (48.8)	69 (46.6)	151 (47.8)	67 (37.9)	218 (44.2)
At least one related TEAE, n (%)	54 (32.1)	49 (33.1)	103 (32.6)	32 (18.1)	135 (27.4)
At least one severe TEAE, n (%)	11 (6.5)	16 (10.8)	27 (8.5)	6 (3.4)	33 (6.7)
At least one life-threatening TEAE, n (%)	2 (1.2)	0	2 (0.6)	0	2 (0.4)
At least one SAE, n (%)	6 (3.6)	1 (0.7)	7 (2.2)	2 (1.1)	9 (1.8)
At least one related SAE, n (%)	0	1 (0.7)	1 (0.3)	0	1 (0.2)
At least one TEAE leading to permanent discontinuation of study drug, n (%)	12 (7.1)	15 (10.1)	27 (8.5)	4 (2.3)	31 (6.3)
At least one related TEAE leading to permanent discontinuation of study drug, n (%)	8 (4.8)	13 (8.8)	21 (6.6)	4 (2.3)	25 (5.1)
At least one AE resulting in death, n (%)	0	0	0	0	0

Table 17: Overview of adverse events: SC MNTX-only pool

Parameter	Double Blind Period MNTX (N=316) n (%)	Open Label Period MNTX (N=1295) n (%)
Number (%) of Patients with		
At least one AE, n (%)	159 (50.3)	968 (74.7)
At least one TEAE, n (%)	151 (47.8)	950 (73.4)
At least one related TEAE, n (%)	103 (32.6)	558 (43.1)
At least one severe TEAE, n (%)	27 (8.5)	262 (20.2)
At least one life-threatening TEAE, n (%)	2 (0.6)	9 (0.7)
At least one SAE, n (%)	7 (2.2)	114 (8.8)
At least one related SAE, n (%)	1 (0.3)	4 (0.3)
At least one TEAE leading to permanent discontinuation of study drug, n (%)	27 (8.5)	151 (11.7)
At least one related TEAE leading to permanent discontinuation of study drug, n (%)	21 (6.6)	107 (8.3)
At least one AE resulting in death, n (%)	0	4 (0.3)

A more comprehensive evaluation of the AEs is shown in the following table, including the results from study 3356 only:

Table 18: Number (%) of subjects with TEAEs reported in ≥2% in double-blind phase, study 3356

System Organ Class [a] Preferred Term	Overall P-Value	Treatment MOA-728 12mg QD n=150	MOA-728 12mg QOD n=148	Placebo n=162	Total n=460
Any Adverse Event	0.135	74 (49.3)	67 (45.3)	62 (38.3)	203 (44.1)
Cardiac disorders	0.161	2 (1.3)	5 (3.4)	1 (0.6)	8 (1.7)
Gastrointestinal disorders	0.032*	45 (30.0)	47 (31.8)	32 (19.8)	124 (27.0)
Abdominal distension	0.457	1 (0.7)	3 (2.0)	1 (0.6)	5 (1.1)
Abdominal pain	<0.001***	29 (19.3)	23 (15.5)	6 (3.7)	58 (12.6)
Abdominal pain upper	0.129	2 (1.3)	8 (5.4)	4 (2.5)	14 (3.0)
Diarrhoea	0.027*	9 (6.0)	17 (11.5)	6 (3.7)	32 (7.0)
Flatulence	0.018*	7 (4.7)	0	6 (3.7)	13 (2.8)
Nausea	0.263	13 (8.7)	17 (11.5)	10 (6.2)	40 (8.7)
Vomiting	0.008**	1 (0.7)	11 (7.4)	8 (4.9)	20 (4.3)
General disorders and administration site conditions	0.403	10 (6.7)	14 (9.5)	9 (5.6)	33 (7.2)
Chills	0.169	2 (1.3)	3 (2.0)	0	5 (1.1)
Feeling cold	0.033*	0	3 (2.0)	0	3 (0.7)
Feeling of body temperature change	0.066	0	4 (2.7)	1 (0.6)	5 (1.1)
Oedema peripheral	0.380	1 (0.7)	1 (0.7)	4 (2.5)	6 (1.3)
Infections and infestations	0.417	14 (9.3)	9 (6.1)	9 (5.6)	32 (7.0)
Urinary tract infection	0.803	2 (1.3)	3 (2.0)	2 (1.2)	7 (1.5)
Injury, poisoning and procedural complications	0.556	5 (3.3)	2 (1.4)	4 (2.5)	11 (2.4)
Investigations	0.938	8 (5.3)	9 (6.1)	10 (6.2)	27 (5.9)
Musculoskeletal and connective tissue disorders	0.826	7 (4.7)	6 (4.1)	9 (5.6)	22 (4.8)
Back pain	0.803	2 (1.3)	3 (2.0)	2 (1.2)	7 (1.5)
Nervous system disorders	0.223	16 (10.7)	14 (9.5)	9 (5.6)	39 (8.5)
Dizziness	0.183	5 (3.3)	2 (1.4)	1 (0.6)	8 (1.7)
Headache	0.760	6 (4.0)	5 (3.4)	4 (2.5)	15 (3.3)
Tremor	0.161	2 (1.3)	5 (3.4)	1 (0.6)	8 (1.7)
Psychiatric disorders	0.488	4 (2.7)	7 (4.7)	4 (2.5)	15 (3.3)
Anxiety	1.000	3 (2.0)	3 (2.0)	3 (1.9)	9 (2.0)
Respiratory, thoracic and mediastinal disorders	0.626	4 (2.7)	7 (4.7)	5 (3.1)	16 (3.5)
Rhinorrhoea	0.803	2 (1.3)	3 (2.0)	2 (1.2)	7 (1.5)
Skin and subcutaneous tissue disorders	0.126	15 (10.0)	13 (8.8)	7 (4.3)	35 (7.6)
Hyperhidrosis	0.035*	9 (6.0)	9 (6.1)	2 (1.2)	20 (4.3)
Piloerection	0.029*	1 (0.7)	4 (2.7)	0	5 (1.1)
Vascular disorders	0.523	8 (5.3)	8 (5.4)	5 (3.1)	21 (4.6)
Hot flush	0.665	4 (2.7)	5 (3.4)	3 (1.9)	12 (2.6)
Orthostatic hypotension	0.696	3 (2.0)	1 (0.7)	2 (1.2)	6 (1.3)

No new safety signals were identified in an analysis of SC MNTX-treated patients for TEAEs of special interest that are related to study drug (TEAEs of special interest include all preferred terms [PTs] in the System Organ Classes [SOCs] of cardiac and hepatobiliary disorders and specific selected other events such as GI perforation, dehydration, and hypotension). The incidence of related TEAEs of special interest was low in both SC pools (≤3%) and was similar to the placebo group. The most commonly reported related TEAEs of special interest included palpitations (three patients, MNTX) in the SC double-blind pool, and hypotension (seven patients) and QT prolongation (six patients) in the SC MNTX-only pool (open-label period).

Serious adverse event / deaths / other significant events

No deaths occurred among the 316 MNTX-treated patients in the SC double-blind pool, and four deaths (none related to study drug) occurred among the 1484 patients in the SC MNTX-only pool.

At least one SAE was reported by nine patients (2%) (six MNTX QD, one MNTX QOD, and two placebo) in the SC double-blind pool and by 114 patients (9%) in the SC MNTX-only pool. Related SAEs were reported by one patient (MNTX QOD group) in the double-blind period in Study 3356 (Module 5.3.5.3, ISS, section 3.6.2), by no patients in the open-label period in Study 3356, and by four patients in Study 3358.

The observed SAE incidence in the SC pools did not raise any safety concerns regarding the long-term use of SC MNTX at a fixed dose of 12 mg in patients with non-cancer pain and OIC.

Laboratory findings

Overall, no difference was seen between SC MNTX and placebo in the incidence of TEAEs related to potentially clinically significant values for laboratory tests, vital sign evaluations, or electrocardiogram assessments.

Safety in special populations

An analysis of potential withdrawal symptoms was performed. Table 8 provides a summary of treatment-emergent AEs (TEAEs) by age group during the double blind phase of 3356 and presents evaluation results with and without the GI-related events.

Table 9 provides a summary TEAEs by age group for the long term methylnaltrexone treated phase population (3356 and 3358) also with and without GI related events.

Table 8: Summary of Treatment-Emergent Adverse Events by Age Group* during Double Blind Phase of Study 3356 (Population: Safety)

	Placebo			MNTX		
	< 65 yrs (N = 147)	65 - 74 yrs (N = 13)	75 - 84 yrs (N = 2)	< 65 yrs (N = 276)	65 - 74 yrs (N = 21)	75 - 84 yrs (N = 1)
Total	54 (36.7%)	8 (61.5%)	1 (50.0%)	132 (47.8%)	12 (57.1%)	1 (100.0%)
Fatal	0	0	0	0	0	0
Serious	2 (1.4%)	0	0	6 (2.2%)	0	0
Withdrawal	2 (1.4%)	2 (15.4%)	0	23 (8.3%)	2 (9.5%)	0
SOC GI Disorders	26 (17.7%)	6 (46.2%)	1 (50.0%)	88 (31.9%)	5 (23.8%)	0
AE Potentially Related to OWS [1]	26 (17.7%)	0	0	78 (28.3%)	5 (23.8%)	0
AE Potentially Related to OWS [1] without GI symptoms	10 (6.8%)	0	0	34 (12.3%)	2 (9.5%)	0
CV Events [2]	0	0	0	0	0	0

Table 9: Summary of Treatment-Emergent Adverse Events by Age Group* during Long Term MNTX Treated Phase Population - Studies 3356 and 3358 (Population: Safety)

	Age < 65 yrs (N = 1210)	65 - 74 yrs (N = 125)	75 - 84 yrs (N = 24)
Total	914 (75.5%)	96 (76.8%)	18 (75.0%)
Fatal	3 (0.2%)	1 (0.8%)	0
Serious	100 (8.3%)	8 (6.4%)	4 (16.7%)
Withdrawal	155 (12.8%)	20 (16.0%)	0
SOC GI Disorders	566 (46.8%)	53 (42.4%)	11 (45.8%)
AE Potentially Related to OWS [1]	484 (40.0%)	45 (36.0%)	8 (33.3%)
AE Potentially Related to OWS [1] without GI symptoms	227 (18.8%)	24 (19.2%)	5 (20.8%)
CV Events [2]	4 (0.3%)	1 (0.8%)	1 (4.2%)

Discontinuation due to adverse events

The most commonly reported TEAEs that led to permanent discontinuation of study drug among the MNTX-treated patients in the SC pools were in the GI disorders SOC and the PT hyperhidrosis, consistent with the known safety profile of MNTX.

Post marketing experience

MNTX is authorised in the EU since July 2008 in the treatment of opioid induced constipation in advanced illness adult patients when response to usual laxative therapy has not been sufficient. In the last PSUR covering the period from 28th March 2013 to 27th March 2014 no actions were considered necessary due to safety reasons.

2.5.1. Discussion on clinical safety

The clinical safety of the compound has been documented with the conduct of two studies, one with a 4-week double-blind design, followed by 8 weeks of open-label treatment, and with a long-term one year “pure” open-label safety study. The safety in the new patient population has been documented in a considerable number of patients, which encompasses 316 patients in double-blind treatments, and over 1600 patients in open-label treatment, of which about 1300 patients were treated in a long-term study. Of these over 600 patients were treated for more than 6 months, and 477 patients were treated for at least 48 weeks.

The safety analysis of these studies has mainly shown a confirmation of the known safety profile of the compound, acting primarily on the gastrointestinal tract. The analysis of these adverse events overall shows a similar adverse event profile compared to the one already known from the patients with advanced illness.

The most frequent adverse events in total, and assessed as being causally related to the intake of the compound were – similar to the previously studied patient population with advanced illness and limited life expectancy – diarrhoea, abdominal pain, flatulence nausea and vomiting. In addition, frequently observed events included dizziness, and injection site reactions. In addition to the previously seen

frequent events, hyperhidrosis was seen in this patient population more frequently than in the previous studies population. However, this undesirable effect was already included in the product information.

In addition it has been derived from the analysis of the submitted studies, especially the double blind phase of study 3356, that there are additional adverse events that occur consistently at higher frequencies in the active treatment groups compared to placebo, and for which a reasonable causality can be assumed. These events comprise the events chills, tremor, piloerection, rhinorrhoea, hot flush, palpitation and hyperhidrosis which have therefore been added to 4.8 of the SmPC summarised as mild withdrawal-like symptoms with the frequency “common”.

The MAH has also evaluated any development of withdrawal symptoms by the application of validated scales, and of the development of “breakthrough” pain during the treatment. These did not give rise for concern, apart from the fact that the potential withdrawal effect of perspiration was indicating a slight increase of this dimension of the respective withdrawal symptom scale (OOWS). This is observed to be in accordance to the observed higher frequency of the above mentioned withdrawal like symptoms chills, tremor, piloerection, rhinorrhoea, hot flush, and, of course the hyperhidrosis and “mild opioid- withdrawal like symptoms” was included as an identified risk into the RMP.

There were no deaths observed during the short-term studies, and the four deaths observed during the long-term study could clearly not be attributed to be causally related to the intake of MNTX. Similarly, from the rare number of events observed being serious, no additional concerns compared to the previously known safety profile can be concluded. Also analysis of laboratory markers and most of the vital signs did also not reveal further concerns previously unknown.

The applicant analysed the age relation of adverse events for the categories of GI disorders as a whole, the mild withdrawal symptoms, and for cardiovascular events which did not show a clear pattern of different risks for older patients. An altered risk-profile in older populations was not observed.

2.5.2. Conclusions on clinical safety

The data presented for the additional patient population to be treated with the compound do overall confirm the known safety profile of the compound. Mild “withdrawal”-like symptoms in patients taking opioids, have been added to 4.8 of the SmPC and were included as an identified risk into the RMP.

2.5.3. PSUR cycle

The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 4.3 is acceptable. However, the RMP is to be updated with the finalised SPC wording to reflect the correct routine risk minimisation measures. The PRAC endorsed PRAC Rapporteur assessment report is attached.

After inclusion of the final SmPC wordings as requested by the CHMP, the CHMP approved vs. 4.5 of the RMP with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Gastrointestinal events
	Gastrointestinal perforation
	Needle issue
	Mild opioid withdrawal-like symptoms
Important potential risks	Potential for Off-label use
	Potential for Medication errors
	Potential for Misuse
	Potential for Breakthrough pain/opioid withdrawal
Missing information	Paediatric patients
	Pregnant women
	Patients with:
	- Unstable vital signs
	- Gastrointestinal obstruction
	- Non-opioid cause of bowel dysfunction
	- Peritoneal cancer
	- Peritoneal catheter
	- Active diverticulitis
	- Faecal impaction
	- Surgically acute abdomen
	- Faecal ostomies
	Patients with:
	- Diarrhoea/watery stools o Dehydration o Hyponatraemia
	Patients with:
	- Dizziness/orthostatic hypotension o History of falls o Injuries
	Long-term treatment

Pharmacovigilance plans

None

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Gastrointestinal effects	Text in SmPC Listed in Section 4.8	None
Gastrointestinal perforation	Text in SmPC Warning in section 4.4 and listed in section 4.8	None
Mild Opioid Withdrawal-like Symptoms	Text in SmPC Listed in section 4.8 PIL provides additional information regarding these symptoms. Patient information leaflet: Mild opioid-withdrawal-like symptoms (any of the following feeling cold, shivering, runny nose, sweating, hair standing on end, blushing, fast heart beat). Patient information leaflet:	None
Off-label use	Text in SmPC Section 4.1 Therapeutic indication and warning in section 4.4 PIL provides additional information regarding dosing and administration for the patient (originally presented as a patient checklist card)	None
Needle issues	Text in SmPC section 6.5 PIL provides Instructions for preparing and giving the injection to aid the patient. Additional text to be on to the tray cover regarding the retractable needle.	None

Medication errors	Text in SmPC section 4.2 PIL provides Instructions for preparing and giving the injection to aid the patient. Presentation of a single-use vial to limit the total amount of medication available (not more than 12 mg)	Pre-filled syringes containing 8 mg/0.4 mL or 12 mg/0.6 mL solution for injection to minimize the risk of medication errors are planned but not yet available in Europe.
Misuse for illegal purpose	Text in SmPC section 4.1 and warning in section 4.4 PIL includes details of the intended use for the product Product only available as a prescription only medicine.	None
Use in paediatrics	Text in SmPC section 4.2 and Section 5.2	None
Use in pregnant women	Text in SmPC section 4.6 and 5.3 PIL advises patient that use in pregnancy is not recommended	None
Use in patients with unstable vital signs, gastrointestinal obstruction, non-opioid cause of bowel dysfunction, peritoneal cancer, peritoneal catheter, active diverticulitis, faecal impaction, surgically acute abdomen or faecal ostomies	Text in SmPC section 4.4 PIL provides advice on when special care is required in use of Relistor	None
Use in patients with diarrhoea/watery stools (dehydration, hyponatraemia)	Text in SmPC section 4.4 PIL provides advice on when special care is required in use of Relistor	None
Use in patients with dizziness/orthostatic hypotension (history of falls, injuries)	Text in SmPC section 4.7 and listed in section 4.8 PIL advises on use of the product while driving and using machinery and also lists dizziness as a common side	None

Potential for Breakthrough pain/opioid withdrawal	Text in SmPC section 4.8. PIL provides details of this potential issue	None
Long-term use	Text in SmPC Sections 4.4 and 5.1 PIL advises on usual treatment duration with Relistor in advanced illness.	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly (please refer to the full PI in attachment).

2.7.1. User consultation

No user consultation with target patient groups on the package leaflet (PL) has been performed. As the changes proposed in this variation are deemed not to be substantial, further readability testing is not considered to be required.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Relistor demonstrated statistically significant and clinical relevant benefit in the non-cancer population in patients that had inadequate relief despite laxative use at screening prior to study entry.

The proportion of patients with ≥3 RFBMs per week during the 4-week double-blind phase was 59% of the patients in the group receiving daily methylnaltrexone 12 mg ($p<0.001$ vs. placebo), in 61% of those receiving it every other day ($p<0.001$ vs. placebo), and in 38% of the placebo treated patients. Supplementary analysis evaluated the percentage of patients achieving ≥3 complete RFBMs per week and an increase of ≥1 complete RFBM per week in at least 3 of the 4 treatment weeks. This was achieved in 28.7% of the patients in the group receiving daily methylnaltrexone 12 mg ($p<0.001$ vs. placebo), in 14.9% of those receiving it every other day ($p=0.012$ vs. placebo), and in 6.2% of the placebo treated patients.

Prompt induction of laxation in non-cancer patients with OIC could be demonstrated. An increase of overall bowel movement frequency can also be concluded, and most of the combinations of the relevant symptoms did also show an improvement over the observation period of four weeks which are considered clinically relevant. The PAC-SYM (patient assessment of constipation symptoms), a standard scale for the observation of constipation and the PAC-QoL (the respective Quality of Life instrument) did also indicate relevant and significant changes in favour of both doses tested.

Since the pharmacodynamic action of a μ-receptor antagonist in does not depend on the reason why the opioid is given findings in non-cancer patients with OIC are considered transferable to non-palliative care patients with cancer for the proposed fixed single dose for all patients (12 mg) regardless of the body weight. Accordingly the indication statement was summarised to the treatment of OIC when response to usual laxative therapy has not been sufficient in adult patients. Nevertheless, as patients in palliative care might be more vulnerable with resulting differences regarding efficacy and safety of the product the posology for the already granted indication was left unchanged.

Albeit Relistor showed somewhat diminished efficacy in the lower dose group the use of the lower dose can be justified as applications can be increased to up to 7 doses weekly if needed.

The open-label extension study and the open-label long-term safety study show to a sufficient extent that beneficial effects in comparison to baseline can be maintained.

Uncertainty in the knowledge about the beneficial effects

The majority of patients (88%) in the pivotal study were constipated at study entry while taking one or more laxatives supporting a second line indication (when response to usual laxative therapy has not been sufficient) instead of the first line indication initially claimed. The uncertainty on the clinical efficacy in the first line indication was addressed by amending the indication to second line.

Risks

Unfavourable effects

The known risks of the compound, mainly its effects on the gastrointestinal tract and associated with the prompt induction of laxation have been confirmed in the trials conducted for the new indication (or patient population). These effects mainly relate to the occurrence of effects such as abdominal pain and cramping, nausea, diarrhoea, flatulence, and vomiting. CNS related side effects are observed only with an increased rate of dizziness. In rare cases in patients with advanced illness, the compound is known to potentially induced gastrointestinal perforations. Further known effects are hyperhidrosis and injection site reactions ranging from singing, redness, and oedema to a sensation of burning pain. All these risks are adequately described in the product in formation and the RMP.

Reasonable causality can be assumed for observed mild withdrawal-like symptoms like chills, tremor, piloerection, rhinorrhoea, hot flush, palpitation and hyperhidrosis which have therefore been added to 4.8 of the SmPC and added to the RMP as an important identified risk.

Uncertainty in the knowledge about the unfavourable effects

Overall, the known and relatively benign safety profile of the compound has also been observed in the newly submitted studies in the new indication.

Benefit-risk balance

Importance of favourable and unfavourable effects

Opioids are a well-established and effective therapy for patients who are receiving palliative care and moderate to severe non-cancer pain; however, opioids can have significant side effects, the most common of which is constipation. In a multi-country, longitudinal study assessing the burden of OIC in 493 patients with NCP, 94% of patients had infrequent bowel movements and at least moderate GI symptoms despite laxative use, and 27% of patients experienced these symptoms despite the use of 2 or more laxatives. Of the 67% of patients who said they had some benefit from laxatives, 56% said they received little benefit from the treatment.[1] In patients receiving chronic opioids for pain, uncontrolled symptoms of OIC can add to their discomfort and may serve as a barrier to effective pain management, limiting opioid dose or prompting opioid discontinuation.

In addition to the already known side effects from the palliative care patient population mild single withdrawal-like symptoms have been identified as new undesirable effects having only minor clinical relevance. In summary Relistor has a relatively benign profile of unfavourable effects being manageable with the appropriate statement as inserted in the product information.

Benefit-risk balance

Relistor demonstrated statistically significant and clinical relevant benefit in the non-cancer population in adult patients that had insufficient response to usual laxative therapy. Since the pharmacodynamic action of a μ-receptor antagonist does not depend on the reason why the opioid is given findings in non-cancer patients with OIC are considered to be transferable to non-palliative care patients with cancer.

The benefits of Relistor in addressing the disease burden of OIC weighed against its relatively benign side effect profile lead to a positive benefit-risk balance in the claimed indication.

[1] Coyne KS, LoCasale RJ, Datto CJ, Sexton CC, Yeomans K, Tack J. Opioid-induced constipation in patients with chronic noncancer pain in the USA, Canada, Germany, and the UK: descriptive analysis of baseline patient-reported outcomes and retrospective chart review. Clinicoecon Outcomes Res 2014;6:269-81.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) accepted		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II

Extension of Indication to include the treatment of opioid-induced constipation in non-cancer adult patients when response to laxative therapy has not been sufficient; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

This variation leads to amendments to the SmPC and Package Leaflet.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.