(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 December 2016 (08.12.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/193456 A2

(51) International Patent Classification:
A61K 31/485 (2006.01) *A61K 9/20* (2006.01)
A61P 1/10 (2006.01) *A61K 9/24* (2006.01)
A61K 9/16 (2006.01) *A61K 9/48* (2006.01)

(21) International Application Number:
PCT/EP2016/062692

(22) International Filing Date:
3 June 2016 (03.06.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
EP15170570.4 3 June 2015 (03.06.2015) EP
EP15170566.2 3 June 2015 (03.06.2015) EP

(71) Applicant: **DEVELCO PHARMA SCHWEIZ AG** [CH/CH]; Hohenrainstraße 12 D, 4133 Pratteln (CH).

(72) Inventors: **REY, Hélène**; 7A rue du 6ème RIC, 68680 Kembs (FR). **MUNDSZINGER, Olaf**; Am Sattel 17, 79588 Efringen-Kirchen (DE). **GOLFIER, Isabelle**; 23a rue des Alpes, 68490 Bantzenheim (FR). **JAKOB, Silvia**; Felseleweg 7, 79872 Bernau im Schwarzwald (DE). **RUSCH, Oliver**; Malzgasse 5, 4052 Basel (CH). **FISCHER, Marc**; 17 rue du Kelberg, 68220 Hagenthal-Le-Bas (FR). **HOLL, Christian**; In den Neumatten 51, 4125 Riehen (CH).

(74) Agent: **CH KILGER ANWALTSPARTNERSCHAFT MBB**; Fasanenstr. 29, 10719 Berlin (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2016/193456 A2

(54) Title: OPIOID RECEPTOR ANTAGONIST FOR USE IN TREATING PATIENTS WITH SEVERE CONSTIPATION

(57) Abstract: The present invention relates to a pharmaceutical composition comprising an opioid receptor antagonist, or a derivative or a pharmaceutically acceptable salt thereof, as an active substance, wherein the composition releases the active substance in a prolonged manner. The composition that is suitable for an administration period of at least twelve-hours for the treatment of severe opioid- induced constipation in patients receiving a daily dosage of opioid equivalent to at least 80 mg of morphine.

OPIOID RECEPTOR ANTAGONIST FOR USE IN TREATING PATIENTS WITH SEVERE CONSTIPATION

BACKGROUND

The present invention is in the field of medicine, particularly in the field of treatment of constipation. The invention relates to a composition comprising an opioid receptor antagonist for use in treating a patient with severe constipation, in particular opioid-induced constipation, wherein the dosage of said opioid is equivalent to at least 80 mg morphine per day.

Constipation is a major symptom of bowel malfunction. Long-term consequences of constipation can increase morbidity and mortality as well as deterioration of quality of life. Chronic constipation can result in haemorrhoid formation, rectal pain and burning, bowel obstruction and potential bowel rupture and death.

Traditional therapies for constipation include bulking agents, stool softeners, stimulant laxatives, and osmotic agents, but the effects of such therapies are nonspecific and are often generating diarrhoea or cramps and some of these drugs cause severe side effects. Furthermore, these conventional measures are sometimes insufficient for some patients.

In some patients the constipation can be opioid induced. Opioid-induced constipation is predominantly due to the activity of gastrointestinal μ-opioid receptors. Selective inhibition of these peripheral receptors can relieve constipation without compromising centrally mediated effects of opioid analgesia or precipitating withdrawal.

Opioids are the most effective analgesics widely used in patients with severe chronic pain. Their clinical efficacy is often burdened by adverse drug reactions that may influence drug adherence associated with early discontinuation, under-dosing, inadequate analgesia and reduced quality of life. One major health concern is constipation occurring in 80-90 % of the patients on long-term opioid treatment. To avoid efficacy problems and specific signs and symptoms of the bowel dysfunction as haemorrhoid formation, rectal pain, burning or bowel obstruction, non-specific laxatives are frequently prescribed as stool softeners, bowel stimulant, or osmotic agents. Their clinical efficacy, however, is not undisputed and they may produce new problems. A more specific approach to avoid opioid-induced constipation in patients with chronic pain is combination therapy with opioid antagonists that may

prevent the undesired μ-opioid receptor activation along the large intestine without compromising the centrally mediated analgesia or precipitating withdrawal effects. Suitable compounds are methylnaltrexone and naloxone that are either not absorbed from the gut lumen, do not pass the blood-brain barrier or are being inactivated along the "first-pass" absorption route. Subcutaneous methylnaltrexone (MNTX-SC) is approved in palliative care for the acute treatment of opioid induced constipation. The quaternary ammonium compound does not cross the blood-brain-barrier; consequently, it does not antagonize the central effects and acts only in the periphery. After subcutaneous administration, it induces predominantly a short-term laxative effect on constipation rather than the desired prevention of opioid-induced bowel dysfunction.

There is also evidence that, despite its very low bioavailability, oral methylnaltrexone antagonizes the morphine-induced delay of intestinal transit time. In these studies, the pharmacodynamic effect and the systemic exposure were not correlated. Despite higher serum concentrations, methylnaltrexone as immediate-release formulation (MNTX-IR) provided lower efficacy compared to the extended-release formulation (MNTX-ER). However, the pharmacodynamics results with oral methylnaltrexone formulations are preliminary and may be misleading as the changes in intestinal motility were evaluated using the lactulose hydrogen breath test which is a measure for small intestinal transit (oro-cecal transit time, OCT). It has to be considered that 10 g of the osmotic active lactulose may exert own laxative effects and may accelerate OCT.

Opioid-induced constipation can be uncomfortable and very painful, and often leads to the discontinuation of the opioid-based therapy, and thus endangers the success of the treatment with the opioids especially in high doses. Since it can be assumed that the opioid-induced constipation is caused directly and locally over the entire intestine through binding to the opioid receptors, this side effect should be eliminated through the use of opioid antagonists. However, the use of opioid antagonists only makes sense if the antagonistic effect is limited to the intestine and does not cancel the main analgesic effect.

Naloxone is a suitable opioid antagonist for the treatment of opioid-induced constipation. Naloxone is rapidly and completely absorbed after oral administration and because the substance is subject to extensive first-pass metabolism, only small amounts of unmetabolised naloxone are available to the system.

The vast majority of the applied substance is found in blood in the form of inactive or only mildly active metabolites such as naloxone-3-glucuronide or beta-6-naloxol.

In suitable doses, naloxone is an ideal candidate for remedying opioid-induced constipation: in the intestine it is present as an active substance and can thus counter the paralysing effect of the opioid on the gastrointestinal tract, while after absorption it is largely metabolised during the first passage in the liver, and thereby becomes inactive. The analgesic effect of the opioids is thus not affected.

Since the paralysis does not only affect the duodenum and the upper part of the small intestine, but the entire gastrointestinal tract, the opioid-induced constipation cannot be treated successfully with a composition that releases the opioid antagonist rapidly. WO 2011/117306 discloses a two-layer tablet, which in one layer contains an opioid agonist, and in another layer an opioid antagonist, wherein the tablet quickly releases both active substances. The advantage of this double-layer is to suppress the side effects of the opioid agonist, but it does not focus on suppression of the opioid-induced constipation.

The combined preparation Targin® is available on the market and comprises a mixture of the opioid agonist oxycodone in the form of a hydrochloric salt, and the opioid antagonist naloxone also in the form of a hydrochloric salt. In this preparation, the active substances are released in a prolonged manner. It is therefore suitable for the parallel treatment of pain and opioid-induced constipation. However, this monolithic formulation has the disadvantage that the release rates of the two active substances are fixed. Individualised treatments are therefore difficult to optimise.

In addition, infusion solutions available on the market for the treatment of opioid poisoning are only naloxone combined preparations, in which naloxone and the opiate are present in a fixed proportion to each other. However, for the treatment of opioid-induced constipation, it would be desirable to have single agent naloxone preparations, since this would allow administering naloxone both independently of the nature of the opiate and in variable doses. The desired quantity of naloxone could therefore be applied, which would lead to an optimal treatment. Naloxone single agent preparations are described in the patent literature, such as in WO 98/25613 A2. However, the release of naloxone from these compositions is dependent on the ambient pH in the gastrointestinal tract. A uniform application of naloxone to the entire gastrointestinal tract, and therefore an optimal treatment, are thus not possible with such products.

Several confounding factors may aggravate constipation during palliative care (dehydration, confusion, drugs, immobility); opioids are a common cause. Prophylaxis can be considered when starting opioid therapy, although common constipation prophylaxis (e.g., fiber, fluids, exercise) may not be sufficient for patients receiving palliative care. In fact, fiber-based laxatives may be dangerous in those with fecal impaction and may result in impaction without adequate water intake.

Also, there is a need to address the problem of resistant opioid-induced constipation. Also, often first line treatments as for example with stool softeners and peristaltic stimulants fail.

In addition, the above products do not address the need of severely constipated patients. Such patients may for example be defined by their colon transit times (CTT). Such patients may have CTTs of 50 hours and more. This is a severe constipation.

Colon transit time is defined as the Whole gut transit (WGT) time minus the Oro-cecal transit time. The WGT time can be determined by any suitable method. However, in a preferred embodiment, the WGT time is determined using radio-opaque markers. OCT time can be determined by any suitable method. Preferably, OCT time is determined by the sulfasalazine/sulfapyridine method (Gramatte, T. et al.; 1991, Int. J. Clin. Pharmacol. Ther. Toxicol.;29(4), 147-150).

DESCRIPTION OF THE INVENTION

The present invention addresses those problems in a first embodiment by a composition comprising an opioid receptor antagonist, or a pharmaceutically acceptable salt thereof, for use in treating a patient with severe constipation, wherein

(i) the antagonist in the composition is prepared in an oral extended release formulation;
(ii) the patient is characterized by a severe opioid-induced constipation;
(iii) wherein the patient is receiving an opiate treatment with a dosage equivalent to at least 80 mg of morphine per day.

Severe constipation is characterized by a WGT of 65 to 180 h, preferably 65 to 150 h, more preferably of 70 to 140 h, even more preferably of 70 to 130 h, yet more preferably of 70 to 120 h, and most preferably of 70 to 110 h. Alternatively, severe constipation is characterized by a WGT of 65 hours or more, preferably 70 h or more and most preferably a WGT of 75 h or more.

The WGT time can be determined by any suitable method. However, in a preferred embodiment, the WGT time is determined using radio-opaque markers.

The feature “the antagonist in the composition is prepared in an oral extended release formulation” means that the composition is an oral composition that releases the antagonist in a prolonged manner.

In preferred embodiments of the invention, the patient is receiving an opiate treatment with a dosage equivalent to at least 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 200, 240, 250, 300, 320, 400, or 500 mg of morphine per day. The higher the dosage of morphine equivalent, the more preferred is the embodiment.

In a more preferred embodiment of the invention the patient is receiving an opiate treatment with a dosage equivalent to 70 to 300 mg morphine, preferably equivalent to 75 to 270 mg morphine, more preferably 85 to 260 mg morphine and most preferably a dosage equivalent to 80 to 250 mg morphine per day.

Preferably, the opioid receptor antagonist is a μ-receptor antagonist.

The daily dosage of a μ-receptor antagonist in the composition can be expressed as naloxone-equivalent dosage. This relation is likely due to the fact that naloxone also belongs to the class of μ-receptor antagonists.

In one embodiment of the invention, the composition comprises the opioid receptor antagonist, or the pharmaceutically acceptable salt thereof, in a dose equivalent to 8 to 60 mg of naloxone, more preferably a dose equivalent to 10 to 56 mg of naloxone, even more preferably a dose equivalent to 12 to 48 mg of naloxone, and most preferably a dose equivalent to 12, 24, 36 or 48 mg of naloxone. Most preferably the daily dosage is equivalent to 24 or 48 mg of naloxone. In one most preferred embodiment the daily dosage is equivalent to 24 mg naloxone. In a second most preferred embodiment the daily dosage is equivalent to 48 mg of naloxone.

In a preferred embodiment of the invention, the composition comprises an opioid receptor antagonist, or the pharmaceutically acceptable salt thereof, in a dose equivalent to 3 to 60 mg of naloxone hydrochloride, more preferably a dose equivalent to 8 to 48 mg of naloxone HCl, even more preferably a dose equivalent to 12 to 48 mg of naloxone HCl. In one embodiment the the composition comprises methylnaltrexone bromide at a dosage of 150 mg, in an alternative embodiment the dosage of methylnaltrexone bromide is 500 mg.

An amount of an opioid or of an opioid antagonist is to be understood as the indicated amount ± 10 %, ± 8 %, ± 5 %, ± 3 %, or more preferably ± 1 %.

In a preferred embodiment, the opioid receptor antagonist is naloxone, methylnaloxone, naloxonesulfonate, methylnaltrexone, naltrexone or any derivative, in particular esthers or sulfonates, or pharmaceutically acceptable salts thereof. More preferably, the opioid receptor antagonist is naloxone or methylnaltrexone, or any derivative or pharmaceutically acceptable salt thereof. In one preferred embodiment, the opioid receptor antagonist is naloxone hydrochloride. In an alternative preferred embodiment, the opioid receptor antagonist is methylnaltrexone, or even more preferably methylnaltrexone bromide.

N-methylnaltrexone bromide (methylnaltrexone) is a quaternary derivative of the pure opioid antagonist naltrexone that does not cross the human blood–brain barrier. Following subcutaneous administration, methylnaltrexone is rapidly absorbed, with peak concentrations achieved at approximately 0.5 hours after administration. The steady-state volume of distribution is 1.1 l/kg. The proportion of methylnaltrexone that binds to plasma proteins is 11-15 % and its terminal half-life was found to be about 8 hours. Accumulation has not been observed with intravenous administration every 6 hours. Methylnaltrexone is primarily eliminated without being metabolised (85% of the administered dose). Approximately half of the dose is excreted in urine and less in faeces. A smaller part of the dose is metabolized to five distinct metabolites; N-demethylation to naltrexone is not a significantly used route.

The inventors found that the composition according to the present invention is in particular suitable for patients, which do not respond to laxatives. Accordingly, in a preferred embodiment the patient is a laxative non-responder.

In a further embodiment objective of the present invention is to provide a solid oral pharmaceutical composition comprising an opioid receptor antagonist, or a pharmaceutically acceptable salt or derivative thereof, as an active substance, wherein the composition releases the opioid receptor antagonist in an extended release formulation, for use in treating patients with severe constipation characterised by a highly increased WGT.

The present invention achieves those objectives by a composition comprising an opioid receptor antagonist, or any pharmaceutically acceptable salt or derivative thereof, for use in treating a patient with severe constipation, wherein:

(i) the antagonist in the composition is prepared in an extended release formulation, and

(ii) the patient is characterized by severe constipation characterized by a WGT of at least 65 h.

Preferably, the composition is a composition that is administered orally.

In a preferred embodiment, the severe constipation is characterized by a WGT of 65 to 180 h, preferably 65 to 150 h, more preferably of 70 to 140 h, even more preferably of 70 to 130 h, yet more preferably of 70 to 120 h, and most preferably of 70 to 110 h. Alternatively, severe constipation is characterized by a WGT of 65 hours or more, preferably 70 h or more and most preferably a WGT of 75 h or more.

An amount of time defined by a number of hours is to be understood as the indicated amount of time in hours ± 10 h, ± 8 h, ± 5 h, ± 3 h, more preferably ± 1 h, and even more preferably ± 0.5 h, but most preferably, the stated time in hours.

In one preferred embodiment, the severe constipation is not an opioid-induced constipation.

In an alternative preferred embodiment, the severe constipation is an opioid-induced constipation.

Opioid-induced constipation can be caused by any opioid analgesic or opioid analgesic analogue, or by any of their salts or mixtures. Examples of such analgesics are the following: alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, besomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, Dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphane, lofentanil, meperidine, meptazinol, metazocine, methadone, metopone, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphane, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, and tramadol, wherein hydrocodone, morphine, hydromorphone, oxycodone, buprenorphine, codeine, fentanyl, levorphanol, meperidine, methadone, levomethadone, and dextromethadone are particularly preferred according to the invention.

The WGT time can be determined by any suitable method. However, in a preferred embodiment, the WGT time is determined using radio-opaque markers.

Alternatively, the severe constipation can be characterized by the colon transit time. CTT is defined as the WGT time minus the OCT time. OCT time can be determined by any suitable method. Preferably, OCT time is determined by the sulfasalazine/sulfapyridine method (Gramatte, T. et al.; 1991, Int. J. Clin. Pharmacol. Ther. Toxicol.;29(4), 147-150).

According to a further embodiment of the invention, the severe constipation is characterized by a colon transit time of at least 55 h. Preferably, the severe constipation is characterized by a colon transit time of 56 to 130 h, more preferably of 60 to 120 h, even more preferably of 65 to 110 h, yet more preferably of 70 to 105 h, and most preferably of 75 to 100 h. Alternatively, severe constipation is characterized by a colon transit time of 56 hours or more, preferably 60 h or more and most preferably a colon transit time of 65 h or more.

Preferably, the opioid receptor antagonist is a μ-receptor antagonist.

In a preferred embodiment, the opioid receptor antagonist is naloxone, methylnaloxone, naloxonesulfonate, methylnaltrexone, naltrexone or any derivative, in particular esthers or sulfonates, or pharmaceutically acceptable salts thereof. More preferably, the opioid receptor antagonist is naloxone or methylnaltrexone, or any derivative or pharmaceutically acceptable salt thereof. In one preferred embodiment, the opioid receptor antagonist is naloxone hydrochloride. In an alternative preferred embodiment, the opioid receptor antagonist is methylnaltrexone, or even more preferably methylnaltrexone bromide.

N-methylnaltrexone bromide (methylnaltrexone) is a quaternary derivative of the pure opioid antagonist naltrexone that does not cross the human blood–brain barrier. Following subcutaneous administration, methylnaltrexone is rapidly absorbed, with peak concentrations achieved at approximately 0.5 hours after administration. The steady-state volume of distribution is 1.1 l/kg. The proportion of methylnaltrexone that binds to plasma proteins is 11-15 % and its terminal half-life was found to be about 8 hours. Accumulation has not been observed with intravenous administration every 6 hours. Methylnaltrexone is primarily eliminated without being metabolised (85% of the administered dose). Approximately half of the dose is excreted in urine and less in faeces. A smaller part of the dose is metabolized to five distinct metabolites; N-demethylation to naltrexone is not a significantly used route.

The daily dosage of a μ-receptor antagonist in the composition can be expressed as naloxone-equivalent dosage. This relation is likely due to the fact that naloxone also belongs to the class of μ-receptor antagonists.

In one embodiment of the invention, the composition comprises the opioid receptor antagonist, or the pharmaceutically acceptable salt thereof, in a dose equivalent to 8 to 60 mg of naloxone, more preferably a dose equivalent to 10 to 56 mg of naloxone, even more preferably a dose equivalent to 12 to 48 mg of naloxone, and most preferably a dose equivalent to 12, 24, 36 or 48 mg of naloxone. Most preferably the daily dosage is equivalent to 24 or 48 mg of naloxone. In one most preferred embodiment the daily dosage is equivalent to 24 mg naloxone. In a second most preferred embodiment the daily dosage is equivalent to 48 mg of naloxone.

One aim of the present invention is to provides a solid oral pharmaceutical composition comprising an opioid receptor antagonist, or a pharmaceutically acceptable salt thereof, as an active substance, wherein the composition releases the active substance in a prolonged manner, and is suitable for an administration period of at least twelve-hours, for the treatment of severe opioid-induced constipation, wherein the dosage of said opioid is equivalent to at least 80 mg of morphine per day.

In one embodiment, the severe constipation is characterized by a WGT of 65 to 180 h, preferably 65 to 150 h, more preferably of 70 to 140 h, even more preferably of 70 to 130 h, yet more preferably of 70 to 120 h, and most preferably of 70 to 110 h.

An amount of time defined by a number of hours is to be understood as the indicated amount of time in hours ± 10 h, ± 8 h, ± 5 h, ± 3 h, more preferably ± 1 h, and even more preferably ± 0.5 h, but most preferably, the stated time in hours.

The *in vitro* release rate is determined using the paddle stirrer apparatus (apparatus 2) with the paddle stirrer method according to Ph. Eur. (European Pharmacopoeia, 7th edition, 3rd supplement, 2.9.3 „Dissolution test for solid dosage forms“, pages 3797-3803) at 75 rpm in 500 ml 0.1 N hydrochloric acid at 37 °C. The amount of released active substance is preferably determined by UV-detection at 220 nm.

The opioid receptor antagonist is provided in an extended release formulation. Preferably the release rate of the opioid receptor antagonist is measured using the paddle stirrer method according to Ph. Eur. at 75 rpm in 500 ml 0.1 N hydrochloric acid at 37 °C. In a preferred embodiment the release rate is 0 % to 75 % in 2 h, 3 % to 95 % in 4 h, 20 % to 100 % in 10 h, 30 % to 100 % in 16 h, 50 % to 100 % in 24 h, and of more than 80 % in 36 h.

In a preferred embodiment the pharmaceutical composition comprises an opioid receptor antagonist such as naloxone, or a pharmaceutically acceptable salt thereof, as an active substance, wherein the composition releases the active substance in a prolonged manner, and the *in vitro* release rate of the active substance, measured using the paddle stirrer method according to Ph. Eur. at 75 rpm in 500 ml 0.1 N hydrochloric acid at 37 °C, is of 0 % to 75 % in 2 h, of 3 % to 95 % in 4 h, of 20 % to 100 % in 10 h, of 30 % to 100 % in 16 h, of 50 % to 100 % in 24 h, and of more than 80 % in 36 h.

It was observed that the composition according to the invention, with its release profile, was suitable for an administration period of at least 12 h for the treatment of opioid-induced constipation. Accordingly, it possesses a relatively high level of patient compliance.

The inventors found that the composition according to the present invention is in particular suitable for patients, which do not respond to laxatives. Accordingly, in a preferred embodiment the patient is a laxative non-responder.

The opioid-induced constipation which can be treated by the composition according to the invention can be caused by any opioid analgesic or opioid analgesic analogue, or by any of their salts or mixtures. Examples of such analgesics are the following: alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, besomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, Dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphane, lofentanil, meperidine, meptazinol, metazocine, methadone, metopone, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphane, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, and tramadol, wherein hydrocodone, morphine, hydromorphone, oxycodone, buprenorphine, codeine, fentanyl, levorphanol, meperidine, methadone, levomethadone, and dextromethadone are particularly preferred according to the invention.

In a particularly preferred embodiment of the invention, the composition releases the active substance independently of the ambient pH of the gastrointestinal tract. This ensures that the entire gastrointestinal tract can be evenly and continuously supplied with the opioid receptor antagonist, or an acceptable salt thereof. A further optimisation of the treatment is thereby achieved. The pH-

independent release of the active substance from the composition of the invention can be achieved through the choice of suitable pharmaceutical excipients that will be known to the person skilled in the art. Local pH values in the gastrointestinal tract are from about 1.2 (in the stomach), to about 6.8 in the colon.

The release of the active substance from the composition of the invention that is independent from the pH of the gastrointestinal tract is preferably understood to mean that the similarity factor f2 between a first *in vitro* release at a pH of 1.2 to 6.8 and a second *in vitro* release at any other pH of 1.2 to 6.8 is larger or equal to 50.

The similarity factor f2 is determined according to SHAH V.P., TSONG Y., SATHE P., & LIU J.P. (1998), "In vitro dissolution profile comparison-statistics and analysis of the similarity factor, f2", Pharmaceutical Research, 15, 889-896. Specifically, the similarity factor f2 is calculated by the following formula:

$$f_2 = 50 * log_{10}([1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2]^{0,5} * 100)$$

In this equation, Rt and Tt represent the released quantities of active substance at time point t at the first and second pH. n is the number of time points. The f2 factor is determined under the following conditions: a) the minimal number of time points for one release is 3 (time point 0 is excluded); b) the time points for the first and the second pH should be equal; c) for each time point, and for each pH, the released quantity is indicated as the mean value of 12 measurements; d) no more than one mean value measured above a release of 85 % can be taken into account for the calculation; e) the relative standard deviation or coefficient of variation of the release at a given pH should be smaller than 20 % for the first time point and smaller than 10 % for the second, and every subsequent time point.

In a further preferred embodiment of the invention, the composition comprises a matrix, which releases the active ingredient in a prolonged manner. The active substance can be released in a prolonged manner inexpensively, particularly when it is contained in a matrix that prolongs its release.

The composition according to the invention may comprise a matrix, which releases an opioid receptor antagonist such as naloxone, or a pharmaceutically acceptable salt thereof, in a prolonged manner. The matrix according to the invention is preferably a so-called scaffold matrix, which can be swelling

or non-swelling, or can be a so-called eroding matrix. The matrix can also have properties of both scaffold and eroding matrixes.

In the case of a scaffold matrix, the active substance is incorporated into the matrix structure. The active substance is gradually dissolved by the digestive juices from the loaded scaffold matrix during the transport through the gastrointestinal tract. At the end of the process, the matrix scaffold is excreted in more or less unchanged form, or in a swollen form. In contrast, with an eroding matrix, the matrix is degraded, or eroded, which leads to active substance particles being exposed at the surface, and dissolved. The release rate therefore depends on the matrix degradation or erosion rate.

For the purpose of forming a largely stable scaffold matrix with an appropriate active substance release rate, a further preferred embodiment of the invention is a composition with a matrix that comprises one or several water-insoluble matrix-forming agents.
Another embodiment of the invention is a composition with a matrix that comprises one or several water-soluble matrix-forming agents.

According to a further preferred embodiment of the invention, the matrix of the composition is water-insoluble.
In an alternative embodiment of the invention, the matrix of the composition is water-soluble.

In another preferred embodiment of the invention, the matrix of the composition comprises one or several matrix-forming agents selected from the group consisting of cellulose esters, polyethylene oxide, polyvinylpyrrolidone/polyvinyl acetate mixtures, methacrylate-acrylate copolymers, waxes, fats such as glycerol esters, and fatty alcohols. The substance classes mentioned here are particularly suitable as matrix-forming agents for the composition of the invention. However, particularly preferred is the use of a mixture of polyvinyl acetate and polyvinylpyrrolidone, and/or a glycerol dibehenic acid ester as matrix-forming agent.

In a further preferred embodiment of the invention, the composition is free of film-coated, opioid receptor antagonist-containing particles, wherein the coating causes the prolonged release of the opioid receptor antagonist.

According to a further preferred embodiment of the invention, the composition can be formed by direct compression, since this is particularly inexpensive.

According to another preferred embodiment of the invention, the composition is in the form of a tablet, capsule, granule, a micro tablet, extruded particles or granules compressed into a tablet.

In a further preferred embodiment of the invention, the composition is designed as a once-a-day formulation, or a twice-a-day formulation.

Regarding the composition which is particularly suited for a twice-a-day administration, the present invention further relates to a solid oral pharmaceutical composition comprising an opioid receptor antagonist, or a pharmaceutically acceptable salt thereof, as an active substance, wherein the composition releases the active substance in a prolonged manner, and the *in vitro* release rate of the active substance, measured using the paddle stirrer method according to Ph. Eur. at 75 rpm in 500 ml 0.1 N hydrochloric acid at 37 °C, is of 5 % to 50 % in 1 h, of 10 % to 75 % in 2 h, of 20 % to 95 % in 4 h, of 40 % to 100 % in 8 h, of more than 50 % in 12 h, of more than 70 % in 18 h, and of more than 80 % in 24 h.

Regarding the composition which is particularly suited for a once-a-day administration, the present invention further relates to a solid oral pharmaceutical composition comprising an opioid receptor antagonist, or a pharmaceutically acceptable salt thereof, as an active substance, wherein the composition releases the active substance in a prolonged manner, and the *in vitro* release rate of the active substance, measured using the paddle stirrer method according to Ph. Eur. at 75 rpm in 500 ml 0.1 N hydrochloric acid at 37 °C, is of 0 % to 50 % in 1 h, of 0 % to 75 % in 2 h, of 10 % to 95 % in 4 h, of 35 % to 100 % in 8 h, of 55 % to 100 % in 12 h, of 70 % to 100 % in 16 h and of more than 90 % in 24h.

Regarding the composition which is particularly suited for a once-a-day administration, the present invention further relates to a solid oral pharmaceutical composition comprising an opioid receptor antagonist, or a pharmaceutically acceptable salt thereof, as an active substance, wherein the composition releases the active substance in a prolonged manner, and the *in vitro* release rate of the active substance, measured using the paddle stirrer method according to Ph. Eur. at 75 rpm in 500 ml 0.1 N hydrochloric acid at 37 °C, is of 0 % to 30 % in 1 h, of 0 % to 40 % in 2 h, of 3 % to 55 % in 4 h, of 10 % to 60 % in 8 h, of 20 % to 75 % in 12 h, of 30 % to 88 % in 16 h, of 50 % to 100 % in 24 h, and of more than 80 % in 36h.

Regarding the composition which is particularly suited for a once-a-day administration, the present invention further relates to a solid oral pharmaceutical composition comprising an opioid receptor antagonist, or a pharmaceutically acceptable salt thereof, as an active substance, wherein the composition releases the active substance in a prolonged manner, and the *in vitro* release rate of the

active substance, measured using the paddle stirrer method according to Ph. Eur. at 75 rpm in 500 ml 0.1 N hydrochloric acid at 37 °C, is of 10 % to 30 % in 1 h, of 17 % to 37 % in 2 h, of 27 % to 47 % in 4 h, of 40 % to 60 % in 8 h, of 50 % to 70 % in 12 h, of 60 % to 80 % in 16 h, and of 80 % to 100 % in 24 h.

In accordance with good patient compliance, a further preferred embodiment of the invention is a composition, wherein the composition is preferably a tablet or a capsule, which has an *in vitro* release rate of the active substance, measured using the paddle stirrer method according to Ph. Eur. at 75 rpm in 500 ml 0.1 N hydrochloric acid at 37 °C, of 0 % to 75 % in 2 h, of 3 % to 95 % in 4 h, of 20 % to 100 % in 10 h, of 30 % to 100 % in 16 h, of 50 % to 100 % in 24 h, and of more than 80 % in 36 h.

A further preferred embodiment of the invention is providing a composition that is suitable for the treatment of opioid-induced constipation for at least 12 h, provided that the composition has an *in vitro* release rate of the active substance of 0 % to 50 % in 2 h, of 5 % to 95 % in 4 h, of 20 % to 90 % in 10 h, of more than 70 % in 18 h, and of more than 80 % in 24 h.

The release rate is, in accordance with the invention, controlled by adjusting the mass ratio of opioid receptor antagonist to matrix-forming agent. In a preferred embodiment, the mass ratio of opioid receptor antagonist to matrix-forming agent is 1:1, more preferably 1:2, more preferably 1:5, more preferably 1:10, more preferably 1:20, even more preferably 1:50, yet more preferably 1:75 and most preferably 1:100.

The composition of the invention is characterised in that through the prolonged release the concentration of the opioid receptor antagonist in the plasma is low. Its maximum plasma concentration (C_{max}) is about 20x lower during the active course compared to a composition without prolonged release, and about 100x lower compared with an intravenously administered composition.

The inhibition of the receptors over the active course is advantageous. In addition to providing the constipation prevention effect of the opioid receptor antagonist, the low bioavailability in the system also ensures a reduced likelihood and/or severity of the side effects.

Since the naloxone inhibitory concentrations (IC_{50}) for opioid receptors (μ, δ and κ) are known, the assessment of the risk factor of a tablet can be calculated with the ratio IC_{50}/C_{max}. With the IC_{50} of μ receptor, the value of IC_{50}/C_{max} for a tablet according to the invention with 48 mg of naloxone is 54. In general, the higher the value of IC_{50}/C_{max}, the lower the risk factor of the tablet according to the invention. Hereafter all values relating to the IC_{50} are for the μ receptor.

In a preferred embodiment, the composition has an IC_{50}/C_{max} value of at least 30. In a more preferred embodiment, the composition has an IC_{50}/C_{max} value of at least 35. In an even more preferred embodiment, the composition has an IC_{50}/C_{max} value of at least 40. In the most preferred embodiment, the composition has an IC_{50}/C_{max} value of at least 50.

In a further embodiment, the composition additionally comprises at least one stabilizer, which protects the active substance. In a preferred embodiment, the at least one stabilizer is selected from the list comprising sulphur dioxide, sodium sulphite, sodium bisulphite, ascorbic acid and its derivatives and tocopherol, as well as its water- and fat-soluble derivatives, such as, for example, tocopherol acetate, sulphites, bisulphites and hydrogen sulphites of alkali, alkaline earth metals or other metals, paraben, BHA, BHT, gallates, as well as lower fatty acids, fruit acids, phosphoric acids, sorbic and benzoic acids as well as their salts, esters, derivatives and isomeric compounds, ascorbyl palmitate, lecithins, mono- and polyhydroxylated benzene derivatives, ethylenediaminetetraacetic acid and salts thereof, citraconic acid, cysteine, L-cysteine, conidendrin, diethyl carbonate, methylenedioxyphenols, cephalin, ß,ß'-dithiopropionic acid, biphenyl and other phenyl derivatives.

In a further embodiment, the composition additionally comprises at least one stabilizer, which protects the matrix. In a preferred embodiment, the at least one stabilizer is selected from the list comprising butylated hydroxytoluol, sulphur dioxide, sodium sulphite, sodium bisulphite, ascorbic acid and its derivatives and tocopherol, as well as its water- and fat-soluble derivatives, such as, for example, tocopherol acetate, sulphites, bisulphites and hydrogen sulphites of alkali, alkaline earth metals and other metals, paraben, BHA, BHT, gallates as well as lower fatty acids, fruit acids, phosphoric acids, sorbic and benzoic acids and their salts, esters, derivatives and isomeric compounds, ascorbyl palmitate, lecithins, mono- and polyhydroxylated benzene derivatives, ethylenediaminetetraacetic acid and their salts, citraconic acid, cysteine, L-cysteine, conidendrin, diethyl carbonate, methylenedioxyphenole, cephalin, ß,ß'-dithiopropionic acid, biphenyl and other phenyl derivatives.

In a further embodiment, the composition comprises at least one additive, wherein the additive is an emetic or a pungent agent drug. In a preferred embodiment, the composition comprises an additive, wherein this additive is a pungent agent, selected from the group comprising Allii sativi bulb, Asari rhizome cum herba, Calami rhizoma, capsici fructus (capsicum} capsici fructus acer (cayenne pepper), Rhizoma Curcumae Longae, Curcumae xanthorrhizae rhizoma, Galangae rhizoma, Semen Myristicae, Piperis nigri fructus (pepper), Sinapis albae (Erucae) Semen, Sinapis nigrae semen, Zedoariae rhizoma and Zingiberis rhizoma, preferably from the group consisting of capsici fructus (capsicum), capsici fructus acer (cayenne pepper) and Piperis nigri fructus (pepper).

In a preferred embodiment, the composition comprises at least one additive, wherein this additive is an emetic. In a preferred embodiment, the emetic is based on one or several substances from radix ipecacuanha (ipecac). In a preferred embodiment, the emetic is based on the substance emetine, in an alternative embodiment, the emetic is apomorphine.

In a further embodiment, the composition comprises a dye. In a preferred embodiment, the dye is selected from a group comprising red iron oxide, black iron oxide and indigo carmine.

In a further embodiment, the composition additionally comprises at least one non-steroid antirheumatic or an antihistamine.

In an alternative embodiment, the composition additionally comprises at least one water-soluble lubricant. In a preferred embodiment, the composition comprises at least one water-soluble lubricant selected from the group comprising adipic acid, fumaric acid, sodium benzoate and macrogol.

EXAMPLES

ORAL COMPOSITION

The following examples are used in conjunction with the drawing to illustrate the invention. It shows:

Fig. 1: Release profiles of the tablets according to examples 1 and 2.

Example 1:

Tablets with the following composition were produced:

Substance	Function	Weight [mg]
Naloxone hydrochloride	Active substance	48.00
Glycerol dibehenic acid ester	Release retardant	204.64
Colloidal silicon dioxide	Flow regulator	19.00
Magnesium stearate	Lubricant	2.36
	Total weight of the tablet	**274.00**

The components naloxone hydrochloride and glycerol dibehenic acid ester were sieved and mixed together. First the sieved Colloidal silicon dioxide and then the magnesium stearate were mixed into the resulting mixture. The thus obtained mixture was pressed into a tablet using a conventional tablet pressing tool.

Example 2:

Tablets with the following composition were produced with the same method as in example 1:

Substance	Function	Weight [mg]
Naloxone hydrochloride	Active substance	12.00
Kollidon® SR	Release retardant	63.16

Vivapur 200	Filler	7.00
Colloidal silicon dioxide	Flow regulator	1.24
Magnesium stearate	Lubricant	0.60
	Total weight of the naloxone layer	**84.00**

Kollidon® SR consisting of 80 wt.-% polyvinyl acetate, 19 wt.-% povidone, 0.8 wt.-% sodium lauryl sulfate and 0.2 wt.-% Colloidal silicon dioxide.

Release profile

The *in vitro* release profiles of the tablets according to examples 1 and 2 were determined using a the paddle stirrer apparatus (apparatus 2) with the paddle stirrer method according to Ph. Eur. (European Pharmacopoeia, 7th edition, 3rd supplement, 2.9.3 „Dissolution test for solid dosage forms“, pages 3797-3803) at 75 rpm in 500 ml 0.1 N hydrochloric acid at 37 °C. The amount of released naloxone was determined by UV-detection at 220 nm.

The *in vitro* release profiles of the tablets according to examples 1 (♦) and 2 (×) are shown in figure 1.

Example 3:

Coated two-layer tablets with the following composition were produced:

Substance	**Function**	**Weight [mg]**
Naloxone layer		
Naloxone Hydrochloride	Active substance	3.00
Kollidon® SR	Release retardant	17.00
Glycerol dibehenic acid ester	Release retardant	4.75
Colloidal silicon dioxide	Flow regulator	0.60
Magnesium stearate	Lubricant	0.15
	Total weight of the naloxone layer	**25.5**
Placebo layer		

Sugar pellets (diameter: 500-600 µm)	Carrier	10.00
Hypromellose	Filler	10.00
microcrystalline cellulose	Filler	10.00
Colloidal silicon dioxide	Flow regulator	0.25
Magnesium stearate	Lubricant	0.25
	Total weight of the placebo layer	**30.50**
	Total weight of the two-layer tablet core	**56.00**
Opadry®	Tablet coating	3.00
	Total weight of the two-layer tablet	**59.00**

The components of the naloxone layer, that is, naloxone hydrochloride, Kollidon® SR, glycerol dibehenic acid ester, colloidal silicon dioxide and magnesium stearate were sieved and blended together to form a first powdery mixture. Further, the components of the placebo layer: sugar pellets, hypromellose, microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate were sieved and mixed together to form a second powdery mixture.

The first and the second mixture were pressed with a conventional two-layer tablet press to obtain the two-layer tablet core. The thus obtained two-layer tablet core was coated to obtain the two-layer tablet.

Example 4:

Coated two-layer tablets of the following composition were produced:

Substance	**Function**	**Weight [mg]**
Oxycodone layer		
Sustained-release oxycodone pellets (containing 24 mg oxycodone HCl)	Active substance	80,00
microcrystalline cellulose	Filler	242,00
Colloidal silicon dioxide	Flow regulator	4,00

Magnesium stearate	Lubricant	4,00
	Total weight of the oxycodone layer	**330,00**
Naloxone layer		
Naloxone hydrochloride	Active substance	48,00
microcrystalline cellulose	Filler	84,00
Kollidon® SR	Release retardant	204,00
Colloidal silicon dioxide	Flow regulator	10,00
Magnesium stearate	Lubricant	2,00
	Total weight of the naloxone layer	**348,00**
	Total weight of the two-layer tablet core	**678,00**
Opadry®	Tablet coating	22,00
	Total weight of the two-layer tablet	**700,00**

The components of the oxycodone layer, that is, sustained release oxycodone pellets, microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate were sieved and blended together to form a first powdery mixture.

Further, the components of the naloxone layer: naloxone hydrochloride, Kollidon® SR, colloidal silicon dioxide and magnesium stearate were sieved and mixed together to form a second powdery mixture.

The first and the second mixture were pressed with a conventional two-layer tablet press to obtain the two-layer tablet core. The thus obtained two-layer tablet core was coated with the coating material Opadry II® that had been dissolved in water at a temperature of 30°C to 50 °C to obtain the two-layer tablet.

The sustained-release oxycodone pellets had the following composition and were prepared as known in the art:

Substance	Function	Weight [mg]
Oxycodone pellets		
Oxycodone hydrochloride	Active substance	3.00
Pellets neutral	Carrier	2.50
Povidone	Binder	0.50
Retardant layer		
Ethylcellulose	Retarding agent	3.00
Hydroxypropylcellulose		0.50
Triethyl citrates		0.50
	Total weight of the sustained release oxycodone pellets	10.00

Kollidon® SR consists of 80 wt.-% polyvinyl acetate, 19 wt.-% povidone, 0.8 wt.-% sodium lauryl sulfate and 0.2 wt.-% Colloidal silicon dioxide.

Opadry II® consists of polyvinyl alcohol, iron oxide or titanium dioxide, Macrogol and talc.

Example 5

Capsules containing micro tablets of 2mm in diameter were produced as follow:

Substance	Function	Weight/capsule [mg]
Micro tablets		
Methylnaltrexone bromide	Active substance	150,00
Povidone		16,50
Colloidal silicon dioxide	Flow regulator	2,25
Magnesium stearate	Lubricant	2,25

Coating of the micro tablets		
Ethylcellulose	Release retardant	16,37
Povidone	Binder	4,91
Propylene glycol	Plasticiser	3,27
Total weight of coated micro tablets /capsule		195,55

The components methylnaltrexone bromide, povidone, colloidal silicon dioxide and magnesium stearate were mixed togethter and compressed on a rotary machine. Micro tablets were further coated with a solution of ethylcellulose, povidone and propylene glycol in a fluid bed processor in order to obtain a sustained release coating.

Example 6

EFFECT OF THE OPIOID ANTAGONIST ADMINISTRATION ON WHOLE GUT TRANSIT TIME

Subjects

The clinical study was performed in 15 German white subjects (11 males, 4 females, age 20-34 years, body mass index 20.3-27.0 kg/ m^2). All subjects were in good health as confirmed by medical histories, physical examination, routine clinical-chemical and hematologic screenings and 12-lead ECG. Three female subjects took hormonal contraceptives regularly and one subject took 300 mg ibuprofen to treat headache 4 days before the administration of study medication. Three subjects were smokers of less than 10 cigarettes per day. 14 subjects drank alcohol occasionally. All were negative in the pre-study screenings for alcohol, drugs, hepatitis-B-virus (HBV) and hepatitis-C-virus (HCV) and human immunodeficiency virus (HIV). Before administration of the study medication, female subjects were screened to be not pregnant and to apply a safe method of contraception. During the entire study period, the subjects avoided strenuous physical activities and did not eat or drink food or beverages containing grapefruit, poppy seeds or alcohol. All participants provided informed written consent before inclusion into the study. The study was approved by the Independent Ethics Committee of the University Medicine Greifswald and by the German Federal Institute for Drugs and Medical Devices (BfArM) and was registered by EudraCT (2009-014357-32) and ClinicalTrials.gov (NCT01596777).

Study protocol

Loperamide is an agonist of μ-opioid receptors in the myenteric plexus without central nervous opioid effects which is known to delay OCT of radiolabeled lactulose that can be reversed by the opioid antagonist naloxone.

Pharmacokinetics of methylnaltrexone and its effects on loperamid-induced experimental constipation were evaluated in a randomized, controlled, five-period, cross-over study with 7 days wash-out between the study periods. Experimental constipation was induced by 4 mg loperamide hydrochloride (Loperamide-ratiopharm®, ratiopharm, Germany) dissolved in 200 ml apple juice which was administered 24, 12 and 1 h before and 12 h after administration of methylnaltrexone placebo capsules (LOP), MNTX-SC (12 mg methylnaltrexone bromide, Relistor®, Wyeth, Berkshire, UK), MNTX-IR (500 mg methylnaltrexone bromide capsules, Develco Pharma Schweiz AG, Switzerland) and MNTX-ER (500 mg methylnaltrexone bromide capsules, Develco Pharma Schweiz AG, Switzerland), respectively. The time of methylnaltrexone administration was defined to be time zero. For control of intestinal transit times in absence of loperamide and methylnaltrexone, 200 ml of pure apple juice and a methylnaltrexone placebo capsule were given at the respective times (Control). Methylnaltrexone placebo capsules were identical in color and shape to MNTX-IR and MNTX-ER which all were swallowed using 200 ml table water; i.e., the clinical study has been performed double-blinded with exception of the MNTX-SC study period. Oro-cecal transit time (OCT) was assessed using the sulfasalazine/sulfapyridine method. For that, 500 mg immediate-release sulfasalazine (Azulfidine®, Pharmacia, Germany) were swallowed with 200 ml table water 2 h after administration of the respective methylnaltrexone study medication to avoid competitive interactions during absorption. The time of first appearance of sulfapyridine in serum was defined to be the OCT (cut-off: 100 μg/ml serum). Whole gut transit time (WGT) was evaluated using a radio-opaque marker method. For that, Colon Transit™ capsules (Medical Instruments Corporation GmbH, Herford, Germany) were swallowed 24, 12 and 1 h before time zero using the 200 ml apple juice for loperamide dosing. Each capsule contains 10 radio-opaque markers of identical shape (e.g. triangles). A Colon Transit™ batch consists of capsules with markers of different shape (e.g. triangles, circles, rings etc.). Our subjects were willing and compliant for sampling stool in single portions immediately after feeling urge without suppressing defecation using tightly closable containers. Then, the number of radio-opaque markers with identical shape was counted in the stool portions after X-ray imaging (Philips Optimus, Philips Healthcare, Hamburg, Germany) using the Agfa PACS Workstation Impact-Version 5.2 (Agfa-Healthcare, Cologne, Germany). From the time of administration of the 3 x 10 radio-opaque markers (3 Colon Transit™ capsules) and the time of their appearance in different stool portions could be reliably concluded on WGT as described below. Colon transit time (CTT) was derived from the difference of WGT and OCT.

For supervised pretreatment with loperamide and Colon Transit™ (mouth checking) and for providing stool samples, the subjects visited the study unit. For pharmacokinetic evaluation and assessment of OCT using the sulfasalazine/sulfapyridine method, the subjects were admitted to the study unit in the evening before and remained there until last blood sampling. After overnight fasting, Colon Transit™, loperamide, the methylnaltrexone study medication or placebo and sulfasalazine were administered as described above. Bed rest lasted from 1.5 h before to 4.5 h after methylnaltrexone administration. Standard meals were served 5, 8 and 13 h after methylnaltrexone administration. The subjects had to eat and drink the same individual amount of food and table water on all study days. To evaluate methylnaltrexone pharmacokinetics and OCT with the sulfasalazine/sulfapyridine method, venous blood was sampled via an indwelling cannula placed in a forearm vein or by individual vein punctures 1.5 h before and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 12, 16, 24 h after administration of the study medication (Smonovette®, Sarstedt, Nürnbrecht, Germany). Urine was collected at 24 h-intervals for 3 days and stool was collected as described above. Serum and urine aliquots were stored at least at -20 °C until quantitative analysis of methylnaltrexone and sulfapyridine, respectively.

Drug analysis

Methylnaltrexone in human serum and urine and sulfapyridine in serum were assayed using a modified liquid chromatopraphy-tandem mass spectrometry (LC-MS/MS) method after protein precipitation of the samples using perchloric acid and with naltrexone as internal standard. [20, 21] The LC-MS/MS system consisted of the Agilent 1100 series HPLC system (Agilent Technologies, Waldbronn, Germany) equipped with the analytical column XTerra MS (2.1 x 100 mm, 3 µm, Waters, Milford, USA) and coupled with the tandem mass spectrometer API 4000 (AB Sciex, Darmstadt, Germany). The method was validated for simultaneous determination of methylnaltrexone and sulfapyridine in serum for the ranges of 0.5 to 250 ng/ml and 0.5 to 500 ng/ml, respectively. In urine, the calibration range for methylnaltrexone was 0.005-1.0 µg/ml.

The chromatograms were evaluated using the Analyst 1.4 software (AB Sciex, Darmstadt, Germany) with the internal standard method using peak-area-ratios for calculation. Between-day and within-day accuracy for the assays of methylnaltrexone in serum and urine and for sulfapyridine in serum was between +8.4 % and -6.9 % of the nominal values. Precision accounted for ±13.1 % of the respective means.

Biometrical evaluation

Pharmacokinetics: Maximum serum concentrations (Cmax) and the time to reach Cmax (Tmax) were obtained from the concentration-time curves. The area under the concentrations-time curve was calculated using the trapezoidal formula with the measured data points from the time of administration until the last quantifiable concentration (AUC_{0-t}) and extrapolated to infinity ($AUC_{0-\infty}$). Terminal elimination half-life ($T_{1/2}$) was estimated by log-linear regression analysis of the terminal slope. Renal clearance (CLR) was derived from cumulative urinary excretion (A_e) of methylnaltexone over $AUC_{0-\infty}$ after subcutaneous and oral administrations.

Intestinal transit times: Oro-cecal transit time (OCT) was defined as the time span between oral administration of sulfasalazine (500 mg immediate-release tablet) and the appearance of its metabolite sulfapyridine in serum (cut-off = 100 µg/ml) which is generated in the cecum by bacterial azo-reduction. Whole-gut transit time (WGT) was assessed by counting the radio-opaque markers with different shapes (Colon TransitTM) in the feces according to formula (1) :

$$(1) \qquad WGT = \frac{\delta_1 + \delta_2 + \delta_3}{3}$$

with δ_{1-3} as derived by formula (2):

$$(2) \qquad \delta_t = \frac{\sum_{n=1}^{n} x_i \cdot t_i}{\sum_{n=1}^{n} x_i}$$

δ_t = mouth to stool transit time of markers type 1, 2, 3

x_i = number of markers type 1, 2, 3 counted at time ti

n = total number of stools

The CTT was evaluated from the difference of WGT and OCT.

Sample size considerations: A post-hoc sample size evaluation using the data of the study (Table 2) and assuming an alpha-error of 0.05 and a power of 80 % has shown that reductions of LOP-delayed OCT, CTT and WGT by 24 %, 20 % and 18 %, respectively, can be confirmed with N=12 subjects.

Statistics: For all samples, arithmetic means (M) ±SD are given. Sample differences were evaluated using the non-parametric Wilcoxon test as appropriate.

All statistical and pharmacokinetic calculations were performed with the SPSS version 12.0 (SPSS Inc., Chicago, U.S.A) and the SAS statistical package (SAS 8.02, SAS Institute Inc., Carry, U.S.A).

RESULTS

MNTX-SC was rapidly absorbed into the blood and reached maximum concentrations between 94.7 and 309 ng/ml after 0.25 to 0.75 hours. The volume of distribution (Vss) ranged between 107 and 712 L and the terminal elimination half-life between 3.4 and 26 hours. 22-51 % of the dose was excreted unchanged into the urine. Renal clearance was between 233-707 ml/min and accounted for 40-51 % of the total body clearance. As renal clearance exceeded 2-6 times the normal values of the glomerular filtration rate in healthy subjects (about 120 mg/min), a substantial part of the parent drug must have been eliminated by tubular secretion (Table 1).

		MNTX-SC	MNTX-IR	MNTX-ER
$AUC_{0-\infty}$	(ng×h/mL)	195 ± 53.2	252 ± 110	47.1 ± 34.7*
C_{max}	(ng/mL)	143 ± 54.4	45.7 ± 25.1	4.63 ± 4.16*
T_{max}	(h)	0.33 ± 0.15	2.57 ± 1.92	3.74 ± 1.38
F	(%)	-	3.11 ± 1.16	0.54 ± 0.31
$T_{½}$	(h)	9.23 ± 5.77	9.99 ± 7.90	n.a.
CL_R	(mL/min)	399 ± 132	404 ± 140	554 ± 415
Ae_{urine}	(mg)	4.45 ± 1.05	5.72 ± 2.76	1.01 ± 0.42*

*p<0.05, compared to MNTX-IR (Wilcoxon test)

Pharmacokinetic characteristics (means ± SD) of methylnaltrexone after subcutaneous injection of 12 mg (MNTX-SC) and single oral administration of 500 mg in immediate-release capsules (MNTX-IR) and extended-release capsules (MNTX-ER) in 15 healthy subjects. T½ after administration of MNTX-ER was not assessed because of the too low number of data points along the terminal elimination slope that were above the limit of quantification.

The absorption of MNTX-IR and MNTX-ER from the gastrointestinal tract was significantly delayed and rather incomplete. MNTX-ER was absorbed with significantly lower rate and was less bioavailable than MNTX-IR. Relative bioavailability of MNTX-IR and MNTX-ER was only 1.53-5.49 % and 0.11-1.24 %, respectively, compared to MNTX-SC. Therefore, systemic exposure (AUC) of MNTX-IR and MNTX-ER was substantially smaller compared to MNTX-SC despite the 42-fold difference in dose (500 mg vs. 12 mg). Systemic elimination of MNTX-IR was not different from MNTX-SC as confirmed by similar terminal elimination halflives and renal clearances. For MNTX-ER, terminal half-life was not assessed

because of low bioavailability and impossibility to assess the terminal slope correctly with an adequate number of data points.

Intestinal transit times in healthy subjects without pretreatment with loperamide and methylnaltrexone (Control) were as follows; WGT ranged between 22.5 and 60.1 h (40.6 ± 9.4 h) whereby OCT accounted for 2.8 and 5.3 h (3.9 ± 0.6 h) and CTT for 17.7-55.6 h (36.7 ± 9.6 h). After pre-treatment with loperamide (LOP), intestinal transit times increased in all 15 subjects (Figure 1). WGT elevated about 1.8-fold to values of 45.9-114 h (73.4 ± 19.9 h) with OCT of 4.0-14.0 h (7.4 ± 3.7 h) and CCT of 33.9-110 h (66.0 ± 20.9 h).

The effects of methylnaltrexone on loperamide-induced constipation was evaluated only in 12 subjects which responded with prolongation of the WGT by >20.5 h (>25 % quartile of all WGT differences between Control versus LOP in 15 subjects). In this group of "LOP-responders", the WGT extended by 20.6-74.1 h (37.8 ± 19.1 h) with 0.50-10.5 h (3.08 ± 3.30 h) being caused by prolongation of the OCT and 18.3-73.6 h (34.8 ± 18.3 h) by CTT. MNTXSC was without significant effect on OCT and CTT. However, OCT was reduced almost to baseline in 8 of our 12 subjects. MNTX-IR also tended to influence OCT (p=0.092) which was reduced to baseline levels in 7 of our 12 subjects. MNTX-ER significantly antagonized loperamide effects on OCT and CTT but, however, not to baseline levels; the transit along the small and large intestine was still significantly prolonged after single dose co-medication of MNTX-ER (Table 2).

		Control	LOP	LOP+ MNTX-SC	LOP+ MNTX-IR	LOP+ MNTX-ER
OCT	(h)	3.92 ± 0.70	7.00 ± 3.55	6.42 ± 3.94	5.29 ± 2.78	5.67 ± 2.97*
WGT	(h)	39.5 ± 8.56	77.3 ± 19.6	71.5 ± 17.2	71.3 ± 21.1	62.3 ± 16.1*/**
CTT	(h)	35.6 ± 9.01	70.3 ± 19.4	65.1 ± 17.9	66.0 ± 21.6	56.7 ± 16.2*/**

p<0.05 Wilcoxon test, *compared to LOP, ** compared to MNTX-IR

Means ± SD of whole-gut transit time (WGT), oro-cecal transit time (OCT) and colon transit time (CTT) before (Control) and after loperamide induced constipation (LOP) and after co-medication of methylnaltrexone by subcutaneous injection of 12 mg (MNTX-SC) and single oral administration of 500 mg in immediate-release capsules (MNTX-IR) and extended-release capsules (MNTX-ER) in 12 healthy subjects which responded to loperamide with prolongation of the whole-gut transit time by >20.5 h (>25 % quartile of the sample).

The study medication was safe and well tolerated. In the entire study, only headache (2x), constipation (1x) and meteorism (1x) were likely or definitely related to the study medication.

Figure legend

Figure 1: Release profile of naloxone from the composition according to the invention; example 1(♦), example 2 (x).

Figure 2: Intestinal transit times in 15 subjects before and after pre-treatment with loperamide (LOP).

Figure 3: Effect of subcutaneous (SC), immediate-release (IR) and extended-release (ER) administration of methylnaltrexone (MNTX) on the oro-cecal transit time (OCT) and the colon transit time (CTT) in 15 subjects upon loperamide (LOP) treatment.

CLAIMS

1. Composition comprising an opioid receptor antagonist, or a derivative or a pharmaceutically acceptable salt thereof, for use in treating a patient with severe constipation, wherein
   (i) the antagonist in the composition is prepared in an oral extended release formulation;
   (ii) the patient is characterized by a severe opioid-induced constipation;
   (iii) wherein the patient is receiving an opiate treatment with a dosage equivalent to at least 80 mg of morphine per day.

2. Composition according to claim 1, wherein the patient is characterized by a whole gut transit time of at 65 to 100 h.

3. Composition according to claims 1 or 2 wherein, the opioid receptor antagonist is selected from the group of naloxone, methylnaltrexone, naltrexone and derivatives in particular esters and sulfonates thereof or a pharmaceutically acceptable salt thereof.

4. Composition according to any of claims 1 to 3, wherein the composition comprises the opioid receptor antagonist, or the derivative or the pharmaceutically acceptable salt thereof, in a dose equivalent to 20 to 28 mg of naloxone.

5. Composition according to any of the claims 1 to 4, wherein the release rate of the opioid receptor antagonist measured using the paddle stirrer method according to Ph. Eur. at 75 rpm in 500 ml 0.1 N hydrochloric acid at 37 °C, is 0 % to 75 % in 2 h, 3 % to 95 % in 4 h, 20 % to 100 % in 10 h, 30 % to 100 % in 16 h, 50 % to 100 % in 24 h, and of more than 80 % in 36 h.

6. Composition according to any of the claims 1 to 5, wherein the composition releases the opioid receptor antagonist independently of the ambient pH of the gastrointestinal tract.

7. Composition according to any of the claims 1 to 6, wherein the composition is a once-a-day formulation.

8. Composition according to any of the claims 1 to 7, wherein the composition is a twice-a-day formulation.

9. Composition comprising an opioid receptor antagonist, or a derivative or a pharmaceutically acceptable salt thereof, for use in treating a patient with severe constipation, wherein
   (i) the antagonist in the composition is prepared in an extended release formulation, and
   (ii) the patient is characterized by severe constipation characterized by a whole gut transit time (WGT) of at least 65 h.

10. Composition according to claim 9, wherein the opioid receptor antagonist is a μ-receptor antagonist.

11. Composition according to claim 9 or 10, wherein the opioid receptor antagonist is naloxone, naloxonesulfonate, methylnaltrexone, naltrexone, or any derivative or pharmaceutically acceptable salt thereof.

12. Composition according to any of the claims 9 to 11, wherein the severe constipation is not an opioid-induced constipation.

13. Composition according to any of claims 9 to 12, wherein the whole gut transit time is determined using radio-opaque markers.

14. Composition according to any of the claims 9 to 13, wherein the patient is characterized by a whole gut transit time of at 65 to 100 h.

15. Composition according to any of claims 9 to 14, wherein the severe constipation is characterized by a colon transit time of 55 to 90 h.

16. Composition according to any of the claims 9 to 15, wherein the composition releases the opioid receptor antagonist independently of the ambient pH of the gastrointestinal tract.

17. Composition according to any of claims 9 to 16, characterised in that the composition is designed as a once-a-day formulation.

18. Composition according to any of claims 9 to 17, characterised in that the composition is designed as a twice-a-day formulation.

Figure 1:

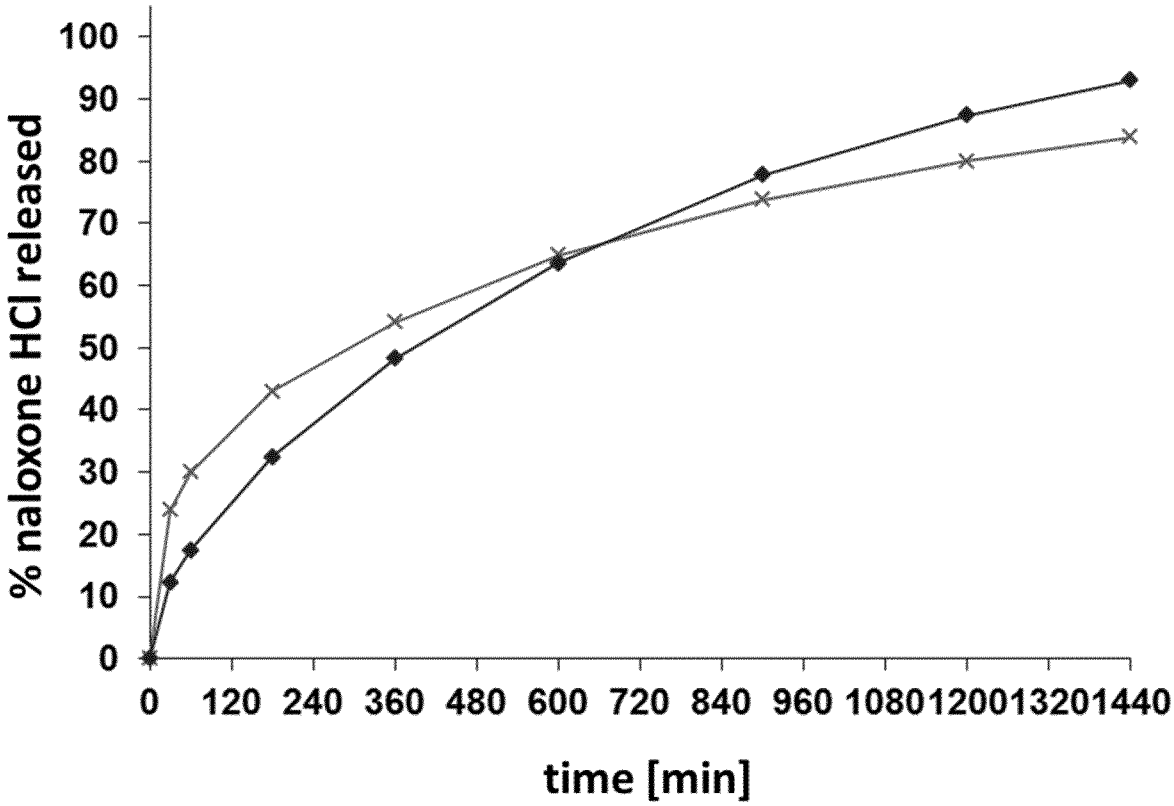

% naloxone HCl released
100
90
80
70
60
50
40
30
20
10
0
0 120 240 360 480 600 720 840 960 1080 1200 1320 1440
time [min]

Figure 2:

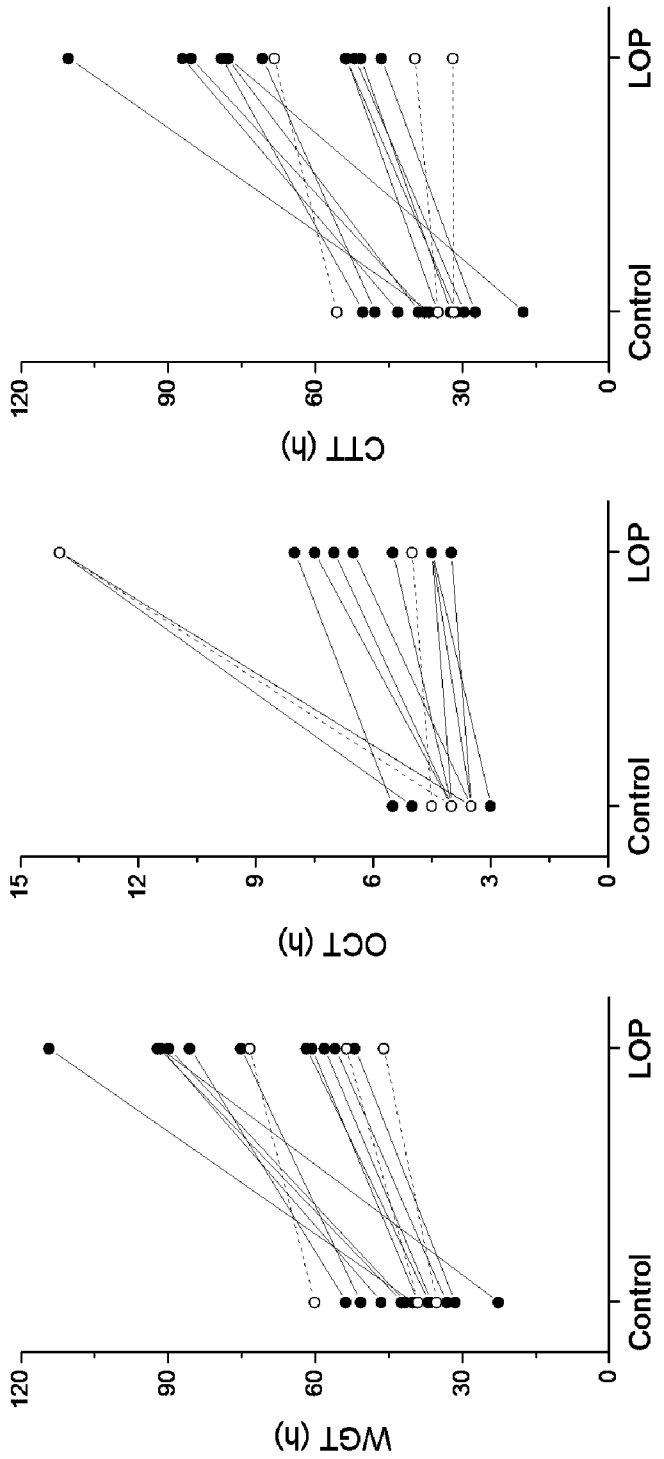
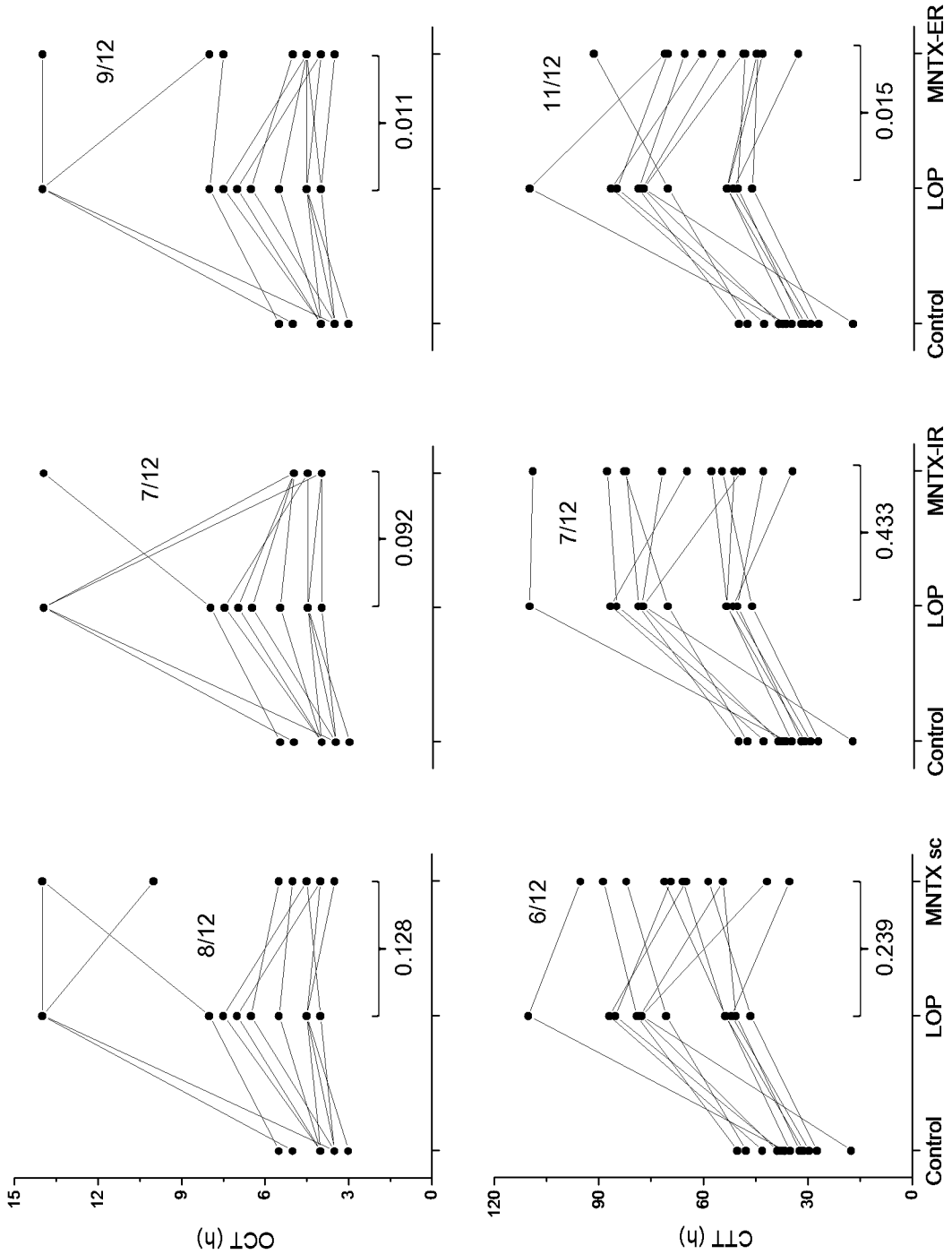

WGT (h)
0
30
60
90
120
Control
LOP
OCT (h)
0
3
6
9
12
15
Control
LOP
CTT (h)
0
30
60
90
120
Control
LOP

Figure 3:


OCT (h)
CTT (h)
15
12
9
6
3
0
120
90
60
30
0
8/12
7/12
9/12
6/12
7/12
11/12
0.128
0.092
0.011
0.239
0.433
0.015
Control
LOP
MNTX sc
MNTX-IR
MNTX-ER