2. SYNOPSIS

Name of Sponsor: Mundipharma Research GmbH & Co. KG	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product:	Referring to Part … of the Dossier	
Name of Active Ingredient: Hydromorphone PR capsules/naloxone PR tablets	Volume: Page:	
Protocol No.: HMX3501	**EudraCT/IND No.:**	

Title of the Study: A confirmatory, placebo-controlled, randomised, double-blind, single-dummy, parallel group, ratio-finding study in constipated pain patients to establish an optimal hydromorphone – naloxone ratio with an improved bowel function and a comparable analgesic efficacy compared to hydromorphone alone.

Investigator(s): This study was conducted at 95 sites in Australia (7 sites), Austria (2 sites), Belgium (3 sites), Czech Republic (10 sites), Denmark (2 sites), Finland (1 site), France (2 sites), Germany (20 sites), Israel (4 sites), Netherlands (1 sites), Poland (7 sites), Romania (4 sites), United Kingdom (13 sites) and USA (19 sites).

Publication (Reference): None

Study Dates:	**Study Status:**	**Phase of Development:**
22 Oct 2009 to 05 Jan 2012	Completed	Phase 3

Objectives:

Primary objective:

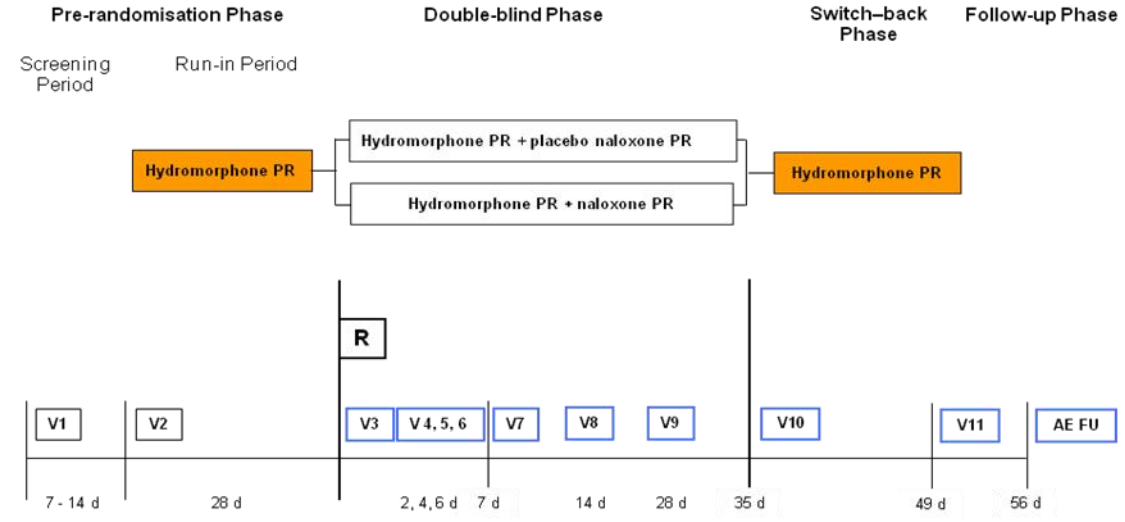
- To investigate whether a hydromorphone/naloxone combination will lead to comparable analgesia (using NRS pain) with a decrease in constipation (BFI) in patients with moderate to severe chronic non-cancer or cancer pain suffering from constipation caused or aggravated by opioids when compared with hydromorphone alone. *(changed to severe to most severe non-cancer or cancer pain by Local Amendment 1 for GE – 08 Sep 2009)*
- To investigate the optimal dose ratio of hydromorphone and naloxone based on findings of the pain and bowel assessments and safety data.

Secondary objectives:

- To assess the frequency of rescue medication use.
- To assess the incidence/frequency of laxative use.
- To assess aspects of constipation [Complete Spontaneous Bowel Movement (CSBMs)].

Methodology: This was a randomised, Double-Blind, single-dummy, parallel-group, multicentre, 14-week study to establish an optimal hydromorphone PR to naloxone PR ratio in subjects taking hydromorphone PR at 8, 24 or 48 mg/day, who had non-cancer or cancer pain that required around-the-clock opioid therapy. This study was composed of two phases: a Pre-randomisation Phase (which consisted of the Screening Period and the Run-In Period) and a Maintenance Phase (which consisted of a Double-Blind Phase, an optional Switch-back Phase and a Follow-up Period). The Pre-randomisation Phase was designed to qualify subjects for participation in the Run-In Period. The Run-In Period was designed to titrate HM PR to analgesic effect (8, 24 or 48 mg/day HM PR) to be used after randomisation, to convert to the study laxative and to qualify subjects for participation in the Double-Blind Phase. The Double-Blind Phase was designed to establish an optimal hydromorphone PR to naloxone PR dose ratio. For those subjects who completed the 5-week Double-Blind Phase, the optional Switch-back Phase was designed to assess the bowel function and analgesic efficacy in subjects receiving hydromorphone PR alone.

Study Design Graphic:



Number of Subjects: It was planned that 400 subjects would be randomised, giving 80 randomised subjects per hydromorphone/naloxone ratio (changed from 450 subjects by Global Protocol Amendment 2 – 04 Jul 2011). In actuality, 852 subjects were screened and 417 subjects were randomised to the study, of which 346 completed the study. Overall baseline characteristics were similar across all ratio groups. In total 255 (61.3 %) female and 161 (38.7%) male subjects were included, a typical gender distribution in chronic pain studies.

Indication and Key Criteria for Inclusion: Males or females of at least 18 years old (with negative pregnancy test), who were receiving WHO step II or step III analgesic medication for the treatment of non-cancer or cancer pain (Criteria changed to severe to most severe non cancer or cancer pain for at least 1 month – Local Amendment 1 for GE – 08 Sep 2009) that required round-the-clock opioid therapy, who had constipation caused or aggravated by opioids (inclusion criteria) but who were not suffering from diarrhoea (exclusion criteria). Subjects must have been treated with a strong opioid for their pain for a minimum of 3 months prior to the screening visit (added by Local Amendment 1 for CZ- 26 Jun 2009).

Test Treatment, Dose, and Mode of Administration:

Test Medication	Dosage Form	Unit Strength	Dosing Frequency	Mode of Administration
Hydromorphone PR	Capsules	4, 8, 24 mg hydromorphone	q12h	Oral
Naloxone PR	Tablet	2, 8, 32 mg naloxone	q12h	Oral

Reference Treatment, Dose, and Mode of Administration:

Test Medication	Dosage Form	Unit Strength	Dosing Frequency	Mode of Administration
Hydromorphone PR	Capsules	4, 8, 24 mg hydromorphone	q12h	Oral
Matched placebo for Naloxone PR	Tablet	2, 8, 32 mg naloxone placebo	q12h	Oral

Concomitant Medication Including Rescue

Analgesic Rescue Medication

Rescue Medication (pain)	Dosage Form	Unit Strength	Dosing Frequency	Mode of Administration
Hydromorphone immediate release (HM IR; i.e., Palladone® Capsules)	Capsules	1.3, 2.6 mg	q4h PRN	Oral

Rescue Medication for constipation

Rescue Medication (laxative)	Dosage Form	Unit Strength	Dosing Frequency	Mode of Administration
Bisacodyl	Tablets	5 mg	q3d PRN (10 mg/d)[#]	Oral

[#]At the discretion of the Investigator, the bisacodyl dose could be lowered (5 mg) if the Investigator/subject felt that the dose was higher than what may be required to provide an adequate bowel movement. If the dose was lowered to 5 mg the lowered dose was counted as a full single dose for this patient

Duration of Treatment: Screening: Up to 14 days; Run-in: up to 28 days; Double-Blind: 5 weeks; Switch-Back: 2 weeks.

Treatment Schedule: The subject's Double-Blind hydromorphone PR dose was the dose the subjects were stabilised on at the end of the Run-In Period (dose range: 8 - 48 mg hydromorphone PR per day).

Subjects who completed the 5 week Double-Blind Phase had the option to enter a 2 week Switch-back Phase, in which they were switched in a direct manner to open-label HM PR alone. Subjects entering the Switch-back Phase were started on the HM PR dose they were assigned to during the Double-Blind Phase. No dose titration was allowed during the Switch-back Phase.

Criteria for Evaluation:

Efficacy Assessments: Primary - Analysis of average pain over the last 24 hours, analysis of Bowel Function Index (BFI)

Secondary - Frequency of rescue medication use, frequency of laxative use, complete spontaneous bowel movements

Safety: Safety was assessed by documentation of adverse events, clinical laboratory results, vital signs, physical examinations, electrocardiograms (ECGs) and Subjective Opioid Withdrawal Scale (SOWS).and recorded on the standard Case Report Form (CRF) pages and Serious Adverse Event (SAE) data form.

Statistical Methods:

Analysis Populations: Enrolled Population: The enrolled population was defined as all subjects who signed informed consent.

Randomised Population: The randomised population was defined as all randomised subjects.

Full Analysis Population: The full analysis population was defined as all randomised subjects who received at least one dose of study medication and had at least one post-baseline primary efficacy endpoint, the BFI.

Per Protocol Population: The per protocol population was defined as all full analysis population subjects without major protocol violations. Major protocol violations were defined during the standardised Determination of Subject Evaluability Assessment (DOSEA) process prior to unblinding.

Run-in Safety Population: The safety population was defined as all enrolled subjects who received at least one dose of open-label HM PR in the Run-in Period.

Double-Blind Safety Population: The safety population was defined as all randomised subjects who received at least one dose of study medication in the Double-Blind Phase.

Switch-back Safety: Subjects who received at least one dose of open-label HM PR during the Switch-back Phase.

Efficacy Analyses: An appropriate HMX ratio was defined as:

- non-inferior analgesic efficacy compared to the HM plus placebo group

and

- superior bowel function based on the BFI value compared to the HM plus placebo group

BFI and Pain intensity were tested separately.

Interim Analyses: An interim analysis of the data was conducted to assess whether the original sample size assumptions were still valid, if the sample size needed to be adjusted, and to determine if the trial needed to be stopped for futility. The interim analysis was carried out when 128 subjects had completed the study i.e. when data was available for approximately 28% of the original sample size. Analyses of both the BFI and Pain Intensity were conducted to assess the efficacy of hydromorphone prolonged-release plus naloxone versus hydromorphone prolonged-release plus naloxone placebo. In the event that either of the efficacy analyses were indicative that hydromorphone prolonged-release plus naloxone would not be non-inferior with respect to pain intensity or not superior with respect to the bowel function index, the study was to be stopped for futility. Assumptions of the original sample size were assessed in an unblinded fashion to examine the variability and dropout rate at the interim analysis. If there was evidence to suggest that the original assumptions were incorrect, the sample size of the study was to be adjusted accordingly. (Added by Global Amendment 1 – 13 Aug 2010).

When the interim analysis was carried out it was concluded that the study was not to be stopped but that the sample size of the study should be slightly reduced, as the SD with Average Pain was found to be 1.5 instead of 1.7 as assumed initially. The interim analysis did not inflate the α-error of the primary analysis.

Safety Analyses: Safety data were summarised descriptively.

Sample Size Rationale: Based on a sequentially rejective test procedure the BFI analysis required a statistically significant finding for the pain parameter.

For 1: With a SD of 1.5 (*changed from 1.7 by Global Protocol Amendment 2 - 04 Jul 2011*) for the Average Pain after 24 hrs and no difference between the compared groups, 58 subjects were included in the per-protocol population so that non-inferiority could be achieved with 90% power.

For 2: Assuming a SD of ≤ 26 (*based on interim analysis*) and a difference of 12 points in the BFI score, *superiority could be demonstrated with 78 subjects per test group (hydromorphone/naloxone ratio), or 80 subjects per test group (full-analysis population) taking into account the low drop-out rate of subjects during the first week after randomisation. (added by Global Protocol Amendment 2 – 04 Jul 2011).*

A sequentially rejective intersection-union test in the order above provided a power of at least 80% versus the composite compound hypothesis.

Non-inferiority was assumed where the one-sided 95% confidence interval of the difference between the treatment means was completely above the non-inferiority bound of 20% (i.e. the lower limit of the 95% CI is completely above 80%). *(changed from a non-inferiority bound of 30% by Global Protocol Amendment 1 – 13 Aug 2010)*

Results:

Efficacy: Irrespective of the ratio between hydromorphone and naloxone, pain scores did not significantly deteriorate during the treatment period but remained unchanged in all treatment groups. Non-inferiority of all hydromorphone/naloxone ratios compared to the hydromorphone/placebo treatment was demonstrated by the statistical analysis, and pain values remained stable until the end of the Switch-back Phase. This was achieved with a very low amount of rescue medication intake in all treatment groups. Based on these results, all hydromorphone/naloxone ratios demonstrated a high and continuous analgesic efficacy being equivalent to the hydromorphone single entity.

Descriptive statistics showed that all hydromorphone/naloxone ratios except for the hydromorphone/placebo group had a clinically relevant improvement in bowel function compared to baseline, as determined by the BFI values. This was further supported by the statistical analysis also reporting statistically significant improvements with all hydromorphone/naloxone ratio groups compared to hydromorphone/placebo.

Overall, the average number of rescue laxative intakes was low, showing that improvement in bowel function was not influenced by the laxative intake and could be attributed to the naloxone component. This is further evidenced by the increase in mean BFI values during the Switch-back Phase, in which subjects did not receive naloxone.

The secondary efficacy objectives supported the results found with the primary objectives. The number of CSBMs increased statistically significantly with all ratio combinations of hydromorphone/naloxone. The BPI Pain Severity Subscale does not indicate a statistically significant difference between the groups, confirming that the analgesic effect of hydromorphone was not affected by the addition of naloxone. Also the average pain over the last 24 hours remained consistent throughout the study for all groups

Safety: There were two deaths (not related to study medication) recorded during safety monitoring of the entire study, one in the Switch-Back Phase and one that occurred outside the study window. There were 4 subjects with 7 SAEs but no deaths during the Double-Blind phase. In total, 277 subjects (66.6%) experienced at least one AE during the Double-Blind phase. There were 623 individual AEs. 170 subjects (40.9%) experienced 324 AEs that were considered by the investigator to be related to study medication. As expected the most common AEs were: nausea (32 subjects in total (7.7%), diarrhoea (22 subjects in total (5.3%), abdominal pain (20 subjects in total (4.8%) and vomiting (15 subjects (3.6%). These are consistent with the expected AE profile of the class of drugs used in this study. The incidence of related GI AEs was equally distributed between the groups. The incidence of diarrhoea was not affected by the ratio of naloxone in the combination. 17 subjects (4.1 %) reported an AE of “drug withdrawal syndrome” with a causal relationship to study medication in the double-blind phase. Incidence rates varied within the ratio and dose groups between 0 and 11.8%, with an overall rate of 4.1%. There was no trend for higher rates of drug withdrawal syndrome in the subgroups with higher naloxone dose or ratio.. The majority of AEs were mild or moderate. The incidence of AEs considered by the investigator to be related to study medication was similar between the dose ratios. There were no clinically important changes in mean haematology, blood chemistry and urinalysis values from baseline to end of study for any treatment group and no notable changes in the number of subjects with abnormal laboratory values from baseline to end of study and no notable differences between the treatment groups.

Conclusions:

- According to the patient's pain assessment and the analgesic rescue medication intake all treatment groups demonstrated the same analgesic efficacy.
- Results of the bowel function parameters confirmed the beneficial effects of naloxone when added to hydromorphone PR and without sacrificing analgesic efficacy.
- The most common AEs were: nausea (32 subjects in total (7.7%), diarrhoea (22 subjects in total (5.3%), abdominal pain (20 subjects in total (4.8%) and vomiting (15 subjects (3.6%).. These are consistent with the expected AE profile of the class of drugs used in this study. The majority of AEs were mild or moderate.
- The incidence of diarrhoea was not affected by the hydromorphone and naloxone ration in the combination.
- The incidence of the drug withdrawal syndrome was not clearly associated with increased naloxone doses or ratios.

Date of the Report: 31 January 2013.