Develco Pharma Schweiz AG

CLINICAL TRIAL REPORT

(SYNOPSIS)

Randomised, double-blind, placebo-controlled, parallel-group, multi-centre, phase III trial to investigate the efficacy, safety and tolerability of Naloxone HCl PR Tablets in patients with opioid induced constipation

Short Title	NAXOS
Product Name	Naloxone HCl 12 mg PR Tablets Naloxone HCl 24 mg PR Tablets
Indication	Opioid induced constipation
Protocol Number	0217/DEV
EudraCT Number	2017-000657-39
Report Version	Final version 1.0
Phase	III
Date First Patient Entered	31-JUL-2017
Date Last Patient Completed	02-MAY-2019
Coordinating Investigator	PD Dr. med. Michael A. Überall Medical Director IFNAP – Institut für Neurowissenschaften, Algesiologie & Pädiatrie Nordostpark 51 90411 Nürnberg, Germany
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Report Issue Date	26-MAR-2020

This trial was performed in compliance with Good Clinical Practices (GCP) and applicable regulatory requirements, including the archiving of essential documents.

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SYNOPSIS

Name of Sponsor: Develco Pharma Schweiz AG	**Individual Trial Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of finished product: Naloxone HCl 12 mg PR Tablets Naloxone HCl 24 mg PR Tablets	**Volume:**	
Name of active ingredient: Naloxone hydrochloride	**Page:**	

Title of trial:

Randomised, double-blind, placebo-controlled, parallel-group, multi-centre, phase III trial to investigate the efficacy, safety and tolerability of Naloxone HCl PR Tablets in patients with opioid induced constipation

Trial number: 0217/DEV

EudraCT number: 2017-000657-39

Sponsor details:

Karin Schmid, Clinical Trial Manager
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Investigators:

A total of 118 active sites and 102 sites with randomised patients

Coordinating Investigator:

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Publication (reference):

None.

Studied period (years):

Date of first enrolment: 31-JUL-2017
Date of last patient completed: 02-MAY-2019

Reporting period:

This report includes the data of the final analysis stage. For the reporting period, please refer to the dates of studied period.

Phase of development: III

Background and rationale:

Opioids, such as morphine, oxycodone, and hydromorphone, are an essential part of the clinical management of chronic non-malignant and malignant pain however, opioids can delay gastric emptying, decrease peristalsis and slow bowel movement. Persistent and severe constipation appears to be the most common adverse effect of chronic opioid therapy. Approximately 40% of patients receiving opioids for non-malignant pain experience opioid induced bowel dysfunction (OBD), including constipation (less than three bowel movements per week), symptoms of cramping, bloating and/or gastro-oesophageal reflux. During recent years, the use of oral naloxone to treat opioid induced constipation (OIC) has attained increasing attention since naloxone can reduce OIC via its competitive antagonism at the peripheral μ-opioid receptors in the gut.

At present there is no oral formulation authorised which contains exclusively naloxone as active substance. Naloxone hydrochloride prolonged-release (HCl PR) Tablets were developed by Develco Pharma Schweiz AG to be freely combined with any other opioid in the indication "treatment of OIC".

This trial was performed to assess the efficacy and safety of Naloxone HCl PR Tablets since there is a clinical need for effective treatment of OIC. Overall, it was anticipated that the patients experience relief in OIC symptoms without major side effects.

Objectives:

Primary:

The primary objective of this trial was to assess the efficacy of Naloxone HCl PR Tablets administered twice daily at total daily dose (TDD) of 24 mg and 48 mg over placebo in the treatment of OIC in terms of overall complete spontaneous bowel movement (CSBM) responder rates.

Secondary:

The secondary objectives of this trial were:

To assess the **efficacy** of Naloxone HCl PR Tablets administered twice daily at TDD of 24 mg and 48 mg in comparison to placebo in terms of:

1. Weekly number of CSBMs and spontaneous bowel movements (SBMs)
2. SBMs (weekly and overall SBM responder rate)
3. Stool consistency according to Bristol Stool Form Scale (BSFS) categories
4. Constipation-related symptoms as determined by Symptoms of Defecation Score (SDS)
5. Bowel Function Index (BFI) score
6. Use of laxative rescue medication
7. Patient assessment of constipation
8. Patient assessment of quality of life
9. Patient and physician satisfaction with treatment
10. Willingness to take drug again
11. Comparison of different opioid/naloxone ratios

The safety objectives were:

To assess the **safety and tolerability** of Naloxone HCl PR Tablets administered twice daily at TDD of 24 mg and 48 mg in comparison to placebo in terms of:

12. Adverse events
13. Pain intensity score
14. Analgesic rescue medication intake
15. Opioid withdrawal scales
16. Vital signs, weight, body mass index (BMI), and physical examination findings
17. Laboratory assessments (i.e., clinical chemistry, haematology, blood coagulation, and urinalysis)
18. Standard 12-lead electrocardiogram (ECG)
19. Comparison of different opioid/naloxone ratios

Methods:

Prospective, randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multi-centre, phase III trial of Naloxone HCl PR Tablets (12 mg and 24 mg) administered twice daily.

The trial consisted of four phases:

Screening phase (Week -4 to Week -3):

The trial started with the screening phase with a maximum duration of 2 weeks.

Confirmation phase (Week -2 to Week -1):

This was followed by a 2-week confirmation phase, during which the diagnosis of OIC and stability of the maintenance opioid dose were to be confirmed.

Double-blind treatment phase (Week 1 to Week 12):

After the confirmation phase, eligible patients were randomised to Naloxone HCl PR Tablets 12 mg or 24 mg twice daily (24 mg or 48 mg TDD) or placebo in a ratio of 1:1:1 and entered the 12-week double-blind treatment phase. Randomisation was stratified by gender, previous laxative use and low/high-dose opioid, in order to achieve similar proportions of patients in each treatment group. (Strata: Female, male. Laxative non-users, laxative users. Low-dose opioid: TDD < 120 mg oral morphine equivalent [ME], high-dose opioid: TDD ≥ 120 mg ME.) All patients had to take two tablets of the trial medication in the morning and two tablets of the trial medication in the evening, i.e. at each intake either

- Naloxone HCl 24 mg PR Tablet plus
  Naloxone HCl 12 mg PR Placebo Tablet, or
- Naloxone HCl 12 mg PR Tablet plus
  Naloxone HCl 24 mg PR Placebo Tablet, or
- Naloxone HCl 24 mg PR Placebo Tablet plus
  Naloxone HCl 12 mg PR Placebo Tablet.

Patients had clinical site visits at the beginning of Week 1 (randomisation/baseline, Visit 3) and at the end of Week 1 (Visit 4), Week 2 (Visit 5), Week 4 (Visit 6), Week 8 (Visit 7), and Week 12 (Visit 8).

Follow-up phase (Week 13-14):

The patients then finally moved to the follow-up phase with a duration of 9 to 14 days.

Number of patients (planned and analysed):

Planned to enrol (=screen):	1492
Enrolled (=screened):	897
Screening failures:	75
Confirmation failures:	259
Planned to randomise:	522
Randomised:	563
Drop-outs:	67
Completed:	496
Analysed (safety):	562
Analysed (efficacy):	563

Diagnosis and main criteria for inclusion and exclusion:

The patients to be included were male or female patients ≥ 18 years of age with OIC under long-term WHO step III opioid therapy for at least 3 months prior to screening for treatment of chronic non-cancer related pain. They had to receive a stable maintenance regimen with one long-acting oral or transdermal WHO step III opioid (except tapentadol) consisting of a TDD of ≥ 40 mg ME for a minimum of 4 weeks prior to screening, with no anticipated change in opioid dose requirement over the proposed trial period. They had to have at least four defined symptoms of constipation with onset after the start of opioid medication for at least the last 4 weeks prior to screening. Additionally, they had to be willing to stop at Visit 2 all laxatives and any other medications used to treat constipation with the exception of provided laxative rescue medication (bisacodyl tablets).
At Visit 2, opioid maintenance regimen had still to be stable and patients had still to be willing to stop any further medications used to treat constipation with the exception of provided laxative rescue medication (bisacodyl tablets).

At Visit 3, all of the criteria mentioned for Visit 2 had still to be met. In addition, all symptoms of confirmed OIC had to be confirmed for the last two weeks prior to Visit 3 and there had to be at least one bowel movement (BM) between Visit 2 and Visit 3. (The calculation of spontaneous bowel movements (SBMs) /week and BMs/week was based on the records in the eDiary.)

Patients were to be excluded due to the following reasons: known or suspected reason for constipation other than OIC, known or suspected medical conditions that might be associated with diarrhoea, intermittent loose stools or constipation, known or suspected gastrointestinal (GI) pathology that might increase the risk of perforation or any form of acute temporary or permanent GI ostomy.

Paediatric regulatory details:

Not applicable

Measures of protection of patients taken:

All patients were closely monitored during the trial. Patients who discontinued trial participation prematurely after completion of Visit 2 were asked to come to the site for an early discontinuation visit (EDV) to exclude the possibility of an adverse event (AE) being the cause. For patients who discontinued from the trial after completing Visit 3 and having received at least one dose of investigational medicinal product (IMP) in addition a follow-up visit 9-14 days after EDV should be scheduled as well, if possible. Serious adverse events (SAEs) which

were still ongoing after the patient's final visit were to be followed-up and follow-up information was to be recorded by the investigators. In case the investigator detected an SAE in a trial patient after the end of the period of observation and considered the event to be possibly related to prior trial treatment or procedures he or she had to contact the sponsor to determine how the SAE was to be documented and reported.

Test products, dose and mode of administration, batch number:

Naloxone HCl PR tablets (12 mg and 24 mg) for twice daily oral administration (in the morning and in the evening, preferably at the same time every day). The TDDs were 48 mg and 24 mg.

Packaging batch number: 212626/1

Batch numbers:

Naloxone HCl PR 12 mg: 17042001

Naloxone HCl PR 24 mg: 17051601

Duration of treatment:

The duration of treatment for the individual patient was 12 weeks.

Reference therapy, dose and mode of administration, batch number:

Corresponding Naloxone HCl PR Placebo Tablets for twice daily oral administration (in the morning and in the evening, preferably at the same time every day).

Packaging batch number: 212626/1

Batch numbers:

Naloxone HCl PR 12 mg placebo: 17032901

Naloxone HCl PR 24 mg placebo: 17041101

Non-investigational medicinal product

Bisacodyl 5 mg gastro-resistant tablets for oral administration, single dose: 5-20 mg (1-4 tablets), authorised medicinal product. The tablets had to be swallowed whole with an adequate amount of fluid [no milk]. The intake was recommended at night.

Packaging batch number: 161868

Endpoints:

Efficacy:

Primary efficacy endpoint was the proportion of overall CSBM Responders.

Overall CSBM response was defined as ≥ 3 CSBMs/week and an increase of ≥ 1 CSBM/week compared to baseline during at least 9 out of the 12 treatment weeks, including all of the last 4 weeks. The primary and selected secondary endpoints were also reported by ratio of opioid to naloxone, expressed as opioid TDD (in ME) divided by naloxone TDD.

The **secondary efficacy endpoints** of this trial were:

1. Proportion of overall SBM Responders (response defined analogously as for CSBMs).
2. Proportion of CSBM Responders by trial week, i.e. having ≥ 3 CSBMs/week and an increase of ≥ 1 CSBM/week compared to baseline.
3. Proportion of SBM Responders by trial week (response defined analogously as for CSBMs).

4. Absolute and relative change of standardised number of CSBMs/week compared to baseline by trial week and overall.
5. Absolute and relative change of standardised number of SBMs/week compared to baseline by trial week and overall.
6. Change from baseline in proportion of type 1 and 2, type 3 and 4, and type 5-7 defecations per week according to BSFS by trial week and overall.
7. CSBM "Sustained Response" defined as ≥ 3 CSBMs/week and an increase of ≥ 1 CSBM/week compared to baseline in all of the last 4 weeks.
8. Absolute and relative change from baseline in each item and the total score of the SDS by trial week and overall.
9. Absolute and relative change from baseline in standardised number of days per week with laxative rescue medication use during the double-blind treatment phase by trial week and overall.
10. Absolute and relative change from baseline in BFI score at the end of Week 1, 2, 4, 8 and 12.
11. Absolute and relative change from baseline in Patient Assessment of Constipation – Symptoms (PAC-SYM) at the end of Week 4, 8 and 12.
12. Absolute and relative change from baseline in Patient Assessment of Constipation - Quality of Life (PAC-QOL) at the end of Week 4, 8 and 12.
13. Absolute and relative change from baseline in EuroQol five dimensions questionnaire (EQ-5D-5L) at the end of Week 4, 8 and 12.
14. Patient and physician satisfaction with treatment at the end of Week 12.
15. Willingness to take drug again assessed at the end of Week 12.

Safety:

The safety endpoints of this trial were:

16. Adverse events (AEs; i.e., incidence, nature, and intensity of AEs, treatment-related AEs, serious AEs (SAEs) and AEs leading to discontinuation) throughout the trial.
17. Absolute and relative change from baseline in the mean visual analogue scale (VAS) pain (recalled pain over the last 12 hours) score by trial week and overall.
18. Absolute and relative change from baseline in standardised number of days per week with analgesic rescue medication use during the double-blind treatment phase by trial week and overall.
19. Observed values and absolute and relative change from baseline in clinical opioid withdrawal scale (COWS) during double blind treatment phase.
20. Observed values and absolute and relative change from baseline in modified subjective opioid withdrawal scale (mSOWS) during double blind treatment phase.
21. Changes from baseline in vital signs (blood pressure, heart rate, body temperature), weight, BMI, and physical examination findings.
22. Changes from baseline in laboratory assessments (i.e., clinical chemistry, haematology, blood coagulation, and urinalysis).
23. Changes from baseline in standard 12-lead ECG.

Statistical methods:

Analysis sets:

The **Enrolled Set** (ES) was defined as all patients who signed informed consent (ICF).

The **Full Analysis Set** (FAS) was defined as all patients who were randomised. Patients in the FAS were analysed as randomised.

The **Per-Protocol Set** (PPS) was defined as all FAS-evaluable patients without major protocol violations that could have an influence on bowel function or bowel function assessment. Patients in the PPS were analysed as treated.

The **Safety Set** (SS) was defined as all randomised patients who received at least one dose of the double-blind trial medication. Patients in the SS were analysed as treated.

Continuous data were summarised by using descriptive statistics - number of patients, number of missing data, mean, standard deviation, median, and range (minimum and maximum). Categorical variables were summarised by using frequency (counts) and proportions.

Analysis of the primary efficacy endpoint

Overall CSBM response rate of Weeks 1 to 12 of Naloxone HCl 24 mg PR Tablets twice daily vs placebo and Naloxone HCl 12 mg PR Tablets twice daily vs placebo was compared. The treatment effect on response rates was analysed using a logistic regression model with treatment, gender, low-/high-dose opioid, and previous laxative treatment as factors. The treatment effect was characterised by odds ratios (naloxone group/placebo group) with associated two-sided 95% confidence intervals (CIs). The primary objective was evaluated in a hierarchical manner (first 48 mg, then 24 mg), to maintain the familywise type I-error rate.

The primary endpoint was analysed in the FAS and in addition on the PPS. The analysis of the PPS was intended to provide supportive evidence of the analysis of the FAS. Further additional sensitivity analysis of overall CSBM Responders' was not performed since investigation of missing data pattern did not reveal any possible issues.

Analysis of secondary efficacy endpoints

All secondary efficacy endpoints were summarised by means of descriptive statistics. In addition to the planned primary efficacy endpoint analysis, further statistical tests for secondary efficacy endpoints to assess the treatment effect were performed and interpreted exploratively.

Secondary efficacy analysis was performed on the FAS.

By-patient data listings were prepared to support all statistical summary tables and for other data reported in electronic case report form or eDiary, as appropriate.

Analysis of safety endpoints

The SS was used for the analysis of the safety data. All safety data obtained in this trial were tabulated descriptively. Treatment emergent adverse events (TEAEs) were summarised by primary system organ class (SOC) and preferred term (PT). Severity and drug-event relationship of TEAEs were summarised separately. All TEAEs were listed. A frequency table was presented for laboratory parameters.

SUMMARY OF RESULTS

PATIENT DISPOSITION:

Out of the 897 enrolled patients (ES), 563 patients were randomised and were included in the FAS. The patients (FAS) were randomised to IMP by country as follows: 149 (26.5%) patients in the UK, 112 (19.9%) patients in Poland, 75 (13.3%) patients in Bulgaria, 59 (10.5%) patients in Czech Republic, 53 (9.4%) patients in Germany, 49 (8.7%) patients in Slovakia and 22 (3.9%, each country) patients in Portugal, Serbia and Spain.

A total of 562 patients took at least one dose of IMP and were included in the SS. The PPS comprised 496 patients. Of 563 randomised patients (FAS), 496 (88.1%) patients completed the trial.

Most FAS patients were of white race (99.5%). Female patients prevailed in this study and comprised 62.0%. The patients' age ranged from 21 to 90 years and the mean (SD) age was 57.6 (11.86) years. The proportion of patients aged over 65 years was higher in the NLX 24 group (32.1%) than in the NLX 48 (23.7%) and in the placebo group (25.8%). The patients' mean (SD) BMI were 29.243 (6.273) kg/m^2.

The most frequent ongoing medical history findings by Preferred Term apart from constipation were hypertension (45.1%), obesity and depression (34.5%, each) and back pain (27.4%).

A total of 189 (33.6%) patients used at least one laxative after start of opioid therapy which was stopped at least 30 days before ICF signature. A total of 361 (64.1%) patients used at least one laxative within the two weeks before ICF signature and a total of 371 (65.9%) patients used at least one prior laxative medication which started and ended prior to or at Visit 2.

All patients used concomitant opioid analgesic medications. The most commonly used opioid analgesic medications in all patients by substance name were oxycodone (39.6%), morphine (23.4%) and fentanyl (20.6%). Other concomitant medications (excluding opioids and laxatives) were taken by 539 (95.7%) of the FAS patients with a slightly higher percentage in the NLX 24 group. The most commonly used medications in all patients by ATC 3rd level subgroup were other analgesics and antipyretics (61.6%), antidepressants (44.8%) and drugs for peptic ulcer and gastro-oesophageal reflux disease (gord) (38.0%).

The compliance to IMP was high, mean (SD) compliance based on drug accountability data was 101.11% (19.368) and a total of 544 (96.6%) patients had a compliance between 80% and 120%. Adherence to patient eDiary reporting was also high. During the treatment phase, a total of 526 (93.4%) patients had an adherence of at least 95% or higher. The mean (SD) adherence was 98.48% (5.098%).

The treatment groups were comparable in most aspects.

EFFICACY RESULTS:

The primary objective of this study was to demonstrate that the administration of Naloxone HCl PR (TDD of 48 mg or 24 mg) is superior to Naloxone HCl PR Placebo (placebo) in terms of the proportion of overall CSBM Responders.

- The number and percentage of CSBM Responders was slightly higher in the NLX 48 group (29 patients, 15.3%) compared to the NLX 24 group (25 patients, 13.4%) and both NLX groups showed a higher number and percentage of overall CSBM Responders compared to placebo (19 patients, 10.2%). No statistically significant differences were observed between the NLX 48 group and placebo group ($p = 0.1648$) nor between the NLX 24 group and placebo group ($p = 0.3725$) in the primary model as well as in the performed sensitivity analysis (NLX 48: $p = 0.1450$ and NLX 24: $p = 0.3467$).
- No statistically significant differences could be observed in the primary analysis of overall CSBM Responders by treatment effect ($p = 0.3786$), gender effect ($p = 0.8113$), opioid TDD type effect ($p = 0.5385$) and previous laxative use effect ($p = 0.1805$). In the sensitivity model analysis of overall CSBM Responders, the treatment effect was also statistically not significant ($p = 0.3430$).
- The **CSBM Responders rate** by trial week fluctuated from baseline to Week 12 (NLX 48: 33.7%, NLX 24: 31.6%, placebo: 27.4%). In each week, the rate of CSBM Responders was higher in both NLX treatment groups compared with the Responder rate in

the placebo group, the highest treatment difference between both NLX groups and the placebo group was observed in Week 8. The percentages of patients with **CSBM sustained response** defined as fulfilling responder criteria for the last four weeks of treatment (Week 9 to Week 12) was higher in both NLX treatment groups (NLX 48: 19.5%; NLX 24: 16.6%) compared with the placebo group (15.6%).

- Other CSBM analyses supported these positive outcomes. The mean numbers of **CSBMs per week** and the mean absolute changes from baseline were higher in both NLX groups compared to the placebo group during the whole treatment phase. Increases to a mean (SD) of 2.3 (2.66) CSBMs/week and to 2.2 (2.75) CSBMs per week, respectively, at Week 12 in the NLX 48 and in the NLX 24 group compared to a mean of 1.8 (2.38) CSBMs per week in the placebo group were observed. A median number of 1.0 CSBM per week was reported for most treatment weeks in the NLX treatment groups compared to a median number of 0 CSBMs per week for most treatment weeks in the placebo group. The overall median number of CSBMs was also higher in the NLX 48 and NLX 24 group (1.208 and 1.167 CSBMs per week, respectively) compared to the placebo group (0.667 CSBMs per week). Median absolute changes from baseline showed a clinically meaningful increase of 1.00 CSBM per week in most treatment weeks in both NLX treatment groups compared with 0.00 CSBMs per week in most treatment weeks in the placebo group. The overall median absolute changes were also higher in the NLX 48 and NLX 24 group (1.167 and 0.833 CSBMs per week, respectively) compared to the placebo group (0.500 CSBMs per week).
- Results from the **responder analysis of spontaneous bowel movements (SBMs)** (defined analogously as for CSBMs) were in line with the results of the CSBM responder analyses. The overall SBMs Responder rates in the NLX 48 and NLX 24 treatment groups (37.9% and 34.2%, respectively) were higher than in the placebo group (31.2%). An adjusted odds ratio of 1.33 and of 1.15 in favour of the NLX 48 group and the NLX 24 group, respectively, did not lead to statistically significant treatment differences. The SBM Responders rate by trial week increased from baseline to Week 12 (NLX 48: 53.7%, NLX 24: 54.6%, placebo: 48.1%). In most treatment weeks, the rate of SBM Responders by week was higher in both NLX treatment groups compared with the Responder rate in the placebo group
- The mean numbers of **SBMs per week** and the mean absolute changes from baseline were higher in both NLX groups compared to placebo during the whole treatment phase. Increases to a mean (SD) of 3.9 (2.99) SBMs/week and to 3.8 (2.99) SBMs per week, respectively, at Week 12 in the NLX 48 and in the NLX 24 group compared to a mean of 3.4 (2.75) SBMs per week in the placebo group were observed. For the whole treatment phase, a median number of 3.0 and 4.0 SBMs per week was reported in the NLX 48 group and of 3.0 SBMs per week in the NLX 24 group compared to a median number of 3.0 SBMs per week only for the last six treatment weeks in the placebo group. Median absolute changes from baseline of 2.0 or 3.0 SBMs per week in all treatment weeks in both NLX treatment groups were reported compared with median changes between 1.0 and 2.0 SBMs per week in the placebo group.

The tendencies between the NLX treatment groups and the placebo group regarding the number of (C)SBM responders and the number of (C)SBMs per week in the NLX treatment groups compared to the placebo group were also reflected by most other secondary efficacy endpoints:

- The evaluation of the **Bristol Stool Form Scale (BSFS)** revealed a softer stool consistency at Week 12 compared to baseline. At baseline notably more patients suffered from constipation (type 1-2) and notably more bowel movements were assigned to constipation in the NLX 48 group (70.0% and 62.2%, respectively) and in the NLX 24 group (71.7% and 63.6%, respectively) compared with the placebo group (57% and 53.4%, respectively). The

percentage of patients who suffered from constipation and the percentage of BMs assigned to constipation decreased notably in both NLX treatment groups from baseline to Week 12 (NLX 48 mg: -18.5% and -33.3%, respectively; NLX 24 mg: -15.6% and -32.2%, respectively). The percentage of patients with constipation in the placebo group increased (+6.3%) and for the percentage of BMs assigned to constipation a lower decrease (-11.5%) was reported. The percentage of patients who reported normal types of stool and the percentage of BMs assigned to normal stools increased notably higher in both NLX treatment groups (NLX 48 mg: +41.9% and +35.7%, respectively; NLX 24 mg: +42.0% and +29.5%, respectively) from baseline to Week 12 compared with the placebo group (+23.3% and +16.1%, respectively).

- All treatment groups showed a clinically meaningful **Bowel Function Index (BFI)** improvement of > 12 at Visit 8. A mean BFI score < 30 was observed in none of the treatment groups. A median score of 30.00 was observed in the NLX 48 group which came close to a normal / regular bowel function. From baseline to Visit 8, higher mean (SD) absolute changes of -36.17 (28.367) and of -37.09 (27.874), respectively, and higher median relative changes of -55.94% and -51.71% were observed in the NLX 48 and the NLX 24 group compared to a lower mean (SD) absolute change from baseline of -26.89 (27.065) and a lower relative median change from baseline of -37.17% in the placebo group.
- The total **Symptoms of Defecation Score (SDS)** improved from baseline to Week 12 with more favourable results in both NLX groups compared to the placebo group. Similar mean [SD] scores (4.838 [4.081] and 4.409 [3.669], respectively) and similar mean absolute changes (-4.896 [4.379] and -4.866 [4.770], respectively) were reported in the NLX 48 and the NLX 24 group compared with a higher mean (SD) score of 6.204 [4.589] and a lower mean absolute change of -3.544 [4.451]) in the placebo group.
- The mean global **Patient Assessment of Constipation - Symptoms scale (PAC-SYM) scores** decreased from baseline to Visit 8 in all treatment groups indicating that patients of all treatment groups experienced less severe constipation. NLX group patients improved more than placebo patients at each visit. From baseline to Visit 8, a mean (SD) absolute change of -1.06 (0.799) and of -1.02 (0.804), respectively, and median relative changes of -58.06% and -61.54%, respectively, were observed in the NLX 48 and the NLX 24 group compared to a lower mean (SD) change from baseline of -0.81 (0.811) and a lower relative median change from baseline of -39.57% in the placebo group.
- For the mean **Patient Assessment of Constipation - Quality of Life scale (PAC-QOL) score**, a decrease > 0.5 points was observed in all treatment groups corresponding to a clinically relevant improvement for the overall PAC-QOL score.
- From baseline to Week 12 **the number of days with laxative rescue medication use** decreased in all treatment groups. The mean number of days with laxative rescue medication use was similar and low in all treatment groups and ranged between 0.4 and 0.5 days in Week 12. At Week 12, the mean absolute change ranged between -1.4 days and -1.2 days.
- From baseline to Visit 8, the percentage of patients with no or slight problems regarding the **EuroQol five dimensions questionnaire (EQ-5D-5L)** categories mobility, self-care, usual activities, pain/discomfort and anxiety/depression increased in all treatment groups with higher percentages in the NLX treatment groups compared to the placebo group for most categories. The percentage of patients with severe or extreme problems decreased in all categories and in all treatment groups. Similar results within a category were observed for self-care, usual activities and anxiety/depression in all treatment groups. For the categories mobility and pain/discomfort, the percentages of patients with severe or extreme problems were lower in both NLX treatment groups compared with the placebo group. The EQ-VAS

reflecting the health status of a patient at a specific visit improved in all treatment groups from baseline to Visit 8, with similar mean VAS scores ranging between 58.2 and 59.6 at Visit 8 and similar mean (SD) absolute changes from baseline ranging between 7.0 (21.40) and 9.7 (25.17) at Visit 8 in the treatment groups.

Subgroups

- When treatment effects were analysed within subgroups (gender, opioid TDD, previous laxative use, route of opioid administration and opioid and opioid/naloxone ratio), treatment groups generally behaved similar to the overall population.
- The subgroup of other opioids (apart from buprenorphine, fentanyl, hydromorphone, morphine and oxycodone) (n = 9) was small and therefore not considered and discussed here.
- No statistical significance in the primary analysis of overall CSBM Responders could be shown in opioid dose subgroup (low-dose/high-dose) and opioid/naloxone ratio subgroup (≤ 1:1, 2:1, 3:1, 5:1 and ≥ 7:1).
- Changes in (C)SBMs were evaluated descriptively for each subgroup. Baseline values were similar in all subgroups and similar to those of the total population for each treatment group.
- When comparing the subgroups within one subgroup category separately for each treatment group for a difference of at least 1 CSBM per week overall in mean and/or median values in combination with a difference of at least 1 CSBM per week in mean and/or median changes from baseline, such differences were observed for the opioid subgroups “oral hydromorphone” (n = 27) vs. all other opioid subgroups in the NLX 48 group in favour of the hydromorphone subgroup. Regarding the opioid/naloxone ratios, relevant differences were observed for a 2:1 ratio between the NLX 48 and NLX 24 group in favour of the NLX 48 group.
- Differences of at least 1 SBM per week overall between the subgroups (within one subgroup category separately for each treatment group) in mean and/or median values in combination with differences of at least 1 SBM per week in mean and/or median changes from baseline were observed for the opioid subgroups “oral hydromorphone” vs. “transdermal buprenorphine”, “transdermal fentanyl” and “oral oxycodone” in both NLX groups in favour of the oral hydromorphone subgroup, for the opioid subgroups “oral morphine” vs. “transdermal buprenorphine” and “transdermal fentanyl” in both NLX groups in favour of the oral morphine subgroups and for the route of opioid administration subgroups “oral” vs. “transdermal” in the NLX 48 group in favour of the oral opioid administration subgroup. Regarding the opioid/naloxone ratios, relevant differences were observed for a 2:1 ratio between the NLX 48 and NLX 24 group in favour of the NLX 48 group.

SAFETY RESULTS:

The mean (SD) **treatment duration** was similar between treatment groups: 75.74 (24.12) days in the NLX 48 group, 77.72 (21.43) days in the NLX 24 group and 78.23 (19.16) days in the placebo group.

A total of 300 patients (53.4%) reported 734 TEAEs during the course of the trial. The highest frequency of patients with TEAEs was observed in the NLX 24 group (57.5%). The frequency of TEAEs was similar in the NLX 48 (51.3%) and placebo group (51.4%).

The most common **primary SOCs** overall were infections and infestations (18.9% patients), gastrointestinal disorders (18.5% patients) and musculoskeletal and connective tissue disorders (11.7% patients).

The most frequent individual TEAEs by **Preferred Term** in total were diarrhoea (5.2%) followed by back pain (4.4%) and viral upper respiratory tract infection (4.1%). The incidences of drug withdrawal syndrome and diarrhoea were slightly higher in the NLX 48 group (4.2% and 6.3%, respectively) and in the NLX 24 group (4.8% and 5.9%, respectively) compared to the placebo group (1.6% and 3.2%, respectively). Frequency differences of more than 5% between the treatment groups were not observed for any individual TEAE.

The proportion of patients who experienced **TEAEs at least possibly related to IMP** was higher in the NLX 48 and NLX 24 group (20.4% patients and 19.9% patients, respectively) than in the placebo group (11.4% patients). Drug withdrawal syndrome and diarrhoea were the most frequent type of such TEAEs (3.6% and 3.2%, respectively) in total.

The mean [SD] duration of all **related TEAEs** was higher in the placebo group (25.2 [30.17] days) compared to the NLX 48 and NLX 24 group (18.7 [26.93] days and 19.6 [24.81] days, respectively).

The vast majority of TEAEs were classified as mild or moderate in **intensity**. In total, 39 severe TEAEs were reported by 30 (5.3%) patients. The incidence of severe TEAEs was similar among treatment groups.

The frequency of **individual TEAEs assessed as severe** was low (5.3% patients) and the proportion of patients with severe TEAEs was comparable in all treatment groups. The most frequently reported severe TEAE by Preferred Term was drug withdrawal syndrome (0.7% patients), followed by diarrhoea, asthma, influenza, back pain and cardiac failure (0.4% patients each). No tendency regarding treatment groups could be observed.

The overall frequency of **serious TEAEs** was low (3.0% patients) and all of these serious TEAEs were considered as not related to IMP. The proportion of serious TEAEs was comparable among treatment groups. One placebo group patient died due to a non-related TESAE (cardiac failure).

The frequency of **TEAEs leading to premature discontinuation** was similar in the NLX 48 and NLX 24 group (11.5% and 9.7%, respectively). In the placebo group, the frequency of TEAEs leading to discontinuation was remarkably lower (4.3% patients).

In total 16 **TEAEs leading to dose interruption** were experienced by 13 patients. The vast majority of the TEAEs leading to premature discontinuation were of mild or moderate intensity.

The number of patients with clinically significant abnormal **laboratory values** was low, no more than two patients per visit and treatment group were reported for haematology, clinical chemistry and blood coagulation parameters. No tendencies regarding treatment groups could be observed.

No relevant changes over time or differences between the groups were observed for **vital signs, ECG or physical examination findings.**

The **mean pain intensity** decreased in both NLX groups and remained nearly constant in the placebo group from baseline to Week 12. In Week 12, the mean pain intensities ranged from 42.479 pixels in the NLX 24 group to 45.690 pixels in the NLX 48 and the placebo group, the mean change from baseline ranged from -1.716 pixels in the placebo group to -5.741 pixels in the NLX 48 group. With regard to the opioid TDD subgroup, differences of more than 5 pixels were observed overall in the NLX 24 group in favour of the opioid low-dose subgroup. The differences in mean absolute changes from baseline between the subgroups were less than 5 pixels in all treatment groups. Regarding the opioid/naloxone ratio differences of more than 5 pixels in mean pain intensities in favour of the NLX 24 group were observed overall between

the treatment groups for a 3:1 ratio and a 5:1 ratio. The differences in mean absolute changes from baseline between the treatment groups were less than 5 pixels for all opioid/naloxone ratios.

No relevant differences between the treatment groups were observed with regard to the mean number of days per week with **analgesic rescue medication use**. The number of days with analgesic rescue medication use was low and remained stable in all treatment groups from baseline to Week 12.

At each timepoint the mean and median **COWS scores** were below 5 points associated with the absence of withdrawal signs. The mean and median COWS scores by opioid TDD and by opioid/naloxone ratio were < 5 points indicating no withdrawals symptoms at each week in each treatment group for each subgroup.

Mean and median scores of **mSOWS** were below 11 at each measurement in all treatment groups, showing absence or mild opioid withdrawal complications. The upper 95% CI was below 11 points at each measurement in all treatment groups except for baseline measurement.

NLX revealed no safety concerns as evaluated by TEAEs, laboratory parameters, vital signs, ECG or physical examinations, pain intensity, analgesic rescue medication use, COWS scores and mSOWS scores.

OTHER RESULTS:

Not applicable.

CONCLUSION:

This is the first study on the treatment of OIC that is fully based on the current recommendations and guideline of the European Medical Association (EMA). It has been designed to fulfil all recommended (and for a subsequent application of approval) mandatory procedures and recommended outcome measures in detail. Study preparation, conduction and data analyses were state of the art and all necessary quality-assurance measures have been taken to guarantee an optimal study performance, both from a methodological and regulatory point of view.

The observed differences between Naloxone HCl PR (TTD of 48 mg or 24 mg) and placebo with regard to the overall CSBM response defined as ≥ 3 CSBMs/week and an increase of ≥ 1 CSBM/week compared to baseline during at least 9 out of the 12 treatment weeks, including all of the last 4 weeks were not statistically significant (NLX 48: $p = 0.1648$ and NLX 24: $p = 0.3725$). None of the analysed factors of the primary analysis or of the sensitivity analysis have a statistically significant effect.

However, the number and percentage of CSBM Responders was slightly higher in the NLX 48 group (15.3%) compared to the NLX 24 group (13.4%) and both NLX groups showed a higher number and percentage of overall CSBM Responders compared to the placebo group (10.2%).

The CSBM Responders rate by trial week increased from baseline to Week 12. In each week, the rate of CSBM Responders was higher in both NLX treatment groups compared with the Responder rate in the placebo group. Also the percentages of patients with CSBM sustained response was higher in both NLX treatment groups compared with the placebo group. The mean numbers of CSBMs per week and the mean absolute changes from baseline were higher in both NLX groups compared to the placebo group during the whole treatment phase. Performed corresponding SBM analyses showed the same tendencies.

All treatment groups showed a clinically meaningful BFI improvement of > 12 at Visit 8. A median score of 30.00 was observed in the NLX 48 group which came close to a normal / regular bowel function. From baseline to Visit 8, higher mean absolute changes and higher median relative changes were observed in the NLX 48 and the NLX 24 group compared to the placebo group.

Other secondary efficacy outcome measures, such as BSFS, SDS, EQ-5D-5L and PAC-SYM support the results obtained for the BFI score and the CSBMs.

For the mean PAC-QOL score, a decrease > 0.5 points was observed in all treatment groups corresponding to a clinically relevant improvement for the overall PAC-QOL score.

The mean number of days with laxative rescue medication use was similar and low in all treatment groups.

NLX revealed no safety concerns as evaluated by TEAEs, laboratory parameters, vital signs, ECG or physical examinations findings, pain intensity, analgesic rescue medication use, COWS scores and mSOWS scores.

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