2. 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 PR tablets (NLX)	Volume:	
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Title of trial:	Randomised, double-blind, placebo-controlled, parallel-group design, multi-centre, dose-escalation phase III trial to investigate the efficacy, safety, and tolerability of Naloxone HCl PR tablets administered in a dose range of 6 mg to 48 mg once daily in patients with opioid induced constipation
Investigators:	Coordinating Investigator: Andreas Schwittay, MD, Studienzentrum Dr. Schwittay, Leipziger Straße 2, 04564 Böhlen, Germany
Trial centres:	Participating countries (active centres with enrolled subjects): Austria: 2 centres; Czech Republic: 7 centres; France: 2 centres; Germany: 11 centres; Hungary: 9 centres; Italy: 1 centre; Poland: 0 centres; Slovakia: 8 centres; Spain: 4 centres; United Kingdom: 3 centres
Publication (reference):	None.
Studied period (years):	date of first enrolment: 24-JUN-2013 date of last subject completed: 01-DEC-2014
Phase of development:	Phase III
Objectives:	
Primary:	The primary objective of this trial was to demonstrate that administration of Naloxone hydrochloride (HCl) PR (prolonged-release) tablets (NLX) once daily is superior to Naloxone HCl PR Placebo (NLX PLA) in the improvement / reversal of opioid-induced constipation (OIC) as determined by the Bowel Function Index (BFI).

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Secondary:	The secondary objectives of this trial were
Efficacy:	1. to assess the efficacy of Naloxone HCl PR tablets administered once daily in comparison to Naloxone HCl PR Placebo in terms of: a. decreased BFI b. increased frequency in bowel movements (bowel movements [BMs], spontaneous bowel movements [SBMs], complete spontaneous bowel movements [CSBMs]) c. improvement of stool consistency as determined by the Bristol Stool Form Scale (BSFS) and symptoms of defecation d. global improvement of OIC as determined by the Patient Assessment of Constipation - Symptoms scale (PAC-SYM) e. changes of constipation-related quality of life as determined by the Patient Assessment of Constipation - Quality of Life scale (PAC-QOL) f. reduction of the number of days with laxative rescue medication 2. to assess the effect of abrupt versus tapered cessation of Naloxone HCl PR tablets administered once daily using BFI; number of BMs, SBMs, and CSBMs; BSFS, Symptoms of Defecation Score and laxative use. 3. to determine a dosing regimen allowing for dose-escalation to an optimal dose of Naloxone HCl PR tablets administered once daily for the treatment of OIC. 4. to assess the effect of Naloxone HCl PR tablets administered once daily for subjects being non-responders to standard laxatives using BFI; number of BMs, SBMs, and CSBMs; BSFS, Symptoms of Defecation Score and laxative use

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Safety:	5. to assess the safety and tolerability of Naloxone HCl PR tablets administered once daily. 6. to assess the (descriptive) non-inferiority regarding opioid induced pain relief (taking pain intensity [PI] assessments and opioid rescue medication requirements into account) of Naloxone HCl PR tablets administered once daily compared to placebo. 7. to assess the lack of systemic effects of Naloxone HCl PR tablets in terms of opioid withdrawal symptoms using the modified Subjective Opioid Withdrawal Scale (SOWS). 8. to assess the rate of treatment failures at Visit 6 due to safety reasons (including effect on PI).	
Methodology:	This trial was a prospective, randomised, double-blind, placebo-controlled, adaptive, parallel-group design, multi-cohort, multi-centre, dose-escalation trial. The trial consisted of six phases: The trial started with the **screening phase** with a maximum duration of two weeks (Week −7 to Week −6, Visit 1 to Visit 2). The open-label opioid **titration phase** had a maximum duration of three weeks (Week −5 to Week −3, Visit 2 to Visit 3). At Visit 2, the subjects discontinued their previous opioid treatment. They were assigned to either oxycodone (Oxy) or hydromorphone (HyMo) trial medication at the investigator's discretion. However, in order to achieve a balanced number of subjects on Oxy and HyMo, one opioid arm was closed earlier. Dosage adjustment was performed every two days, if required, based on the assessments of PI and the use of rescue medication. After completion of the titration phase the trial opioid dose was not to be changed anymore. The single-blind Naloxone HCl PR Placebo **run-in phase** had a fixed duration of two weeks (Week −2 to Week −1, Visit 3 to Visit 4). At Visit 3, the subjects discontinued their previous laxative medication. Subjects received NLX PLA 3 mg once daily	

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for two weeks. Subjects were blinded to NLX PLA treatment. If OIC (according to modified Rome III criteria and BFI), and adequate and stable analgesia were confirmed at the end of the 2-week run-in phase (Visit 4), subjects were randomised to double-blind treatment with investigational medicinal product (IMP) (either NLX or NLX PLA, 2:1 randomisation).

The double-blind dose-escalation / **treatment phase** had a fixed duration of 12 weeks (Week 1 to Week 12, Visit 4 to Visit 11) for all subjects. Subjects started with the lowest total daily dose (TDD) of 6 mg IMP and were treated on this dose level for two weeks. After two weeks, the dose was escalated to 12 mg IMP per day for a further two weeks. Each further escalation step (dose level of 24 mg and 48 mg IMP per day) lasted for at least two weeks.

The decision of IMP dose escalation, de-escalation or treatment failure was based on the evaluation of pain control and tolerability. Once the individual final IMP dose level had been established based on the effect on bowel function, the subject continued to take this IMP dose for at least four weeks from Week 9 until the end of Week 12. After completion of the treatment phase (Visit 11), the subjects were randomised (1:1) to either abrupt or tapered IMP cessation.

The subject moved then to the double-blind **extension phase** with a duration of two weeks (Week 13 to Week 14, Visit 11 to Visit 13). Subjects randomised to abrupt cessation immediately discontinued treatment with IMP at the end of Week 12. Subjects randomised to tapered cessation gradually tapered the IMP treatment.

The subject then finally moved to the **follow-up phase** with a duration of 9 to 14 days (Week 15 to Week 16, Visit 13 to Visit 14).

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Screening Phase	Titration Phase	Run-In Phase	Treatment Phase	Extension Phase	Follow-Up Phase
Any opioid analgesic	Trial opioid (titration)	Trial opioid at a stable dose	Trial opioid at a stable dose	Trial opioid at a stable dose	Any opioid analgesic
Any opioid rescue medication	Trial opioid rescue medication	Trial opioid rescue medication	Trial opioid rescue medication	Trial opioid rescue medication	Any opioid rescue medication
No naloxone within 30 days before V1	No naloxone	**NLX PLA**	**NLX or NLX PLA**	**If tapering off: NLX or NLX PLA**	No naloxone
Any laxative	Any laxative	Trial laxative rescue medications	Trial laxative rescue medications	Trial laxative rescue medications	Any laxative

Number of subjects (planned and analysed):	Planned to randomise: 153 Enrolled: 267 Failed screening: 39 Drop-outs before randomisation: 45 Randomised: 183 Withdrawn during treatment phase: 24 Completed the treatment phase: 159 Analysed (safety): 183 Analysed (efficacy): 183 Of 183 subjects randomised, 121 subjects belonged to the NLX group and 62 to the placebo group. A total of 159 (86.9%) subjects completed the double-blind treatment phase of the trial: 102 (84.3%) NLX subjects and 57 (91.9%) placebo subjects. A total of 158 (86.3%) subjects completed the trial including the extension phase: 102 (84.3%) subjects in the NLX group and 56 (90.3%) subjects in the placebo group.
Diagnosis and main criteria for inclusion:	The subjects to be included in the screening phase were males and females, aged 18 years or over, and had a documented history of constipation induced or worsened by their oral, transdermal or sublingual World Health Organization (WHO) step-II or step-III opioid medication for at least the last four weeks before Visit 1. They required laxatives to have BMs, or had less than three BMs

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	per week when not taking laxatives for at least the last four weeks before Visit 1. The subjects had a documented history of chronic severe non-malignant pain that required around-the-clock opioid therapy and likely to benefit from WHO step-III opioid therapy for the duration of the trial. Subjects suffered from predominantly non-neuropathic pain, as determined by a DN4 Neuropathic Pain Diagnostic Questionnaire score < 4. In accordance with the Protocol Amendment No. 1 for the UK (01-MAR-2013), subjects with transdermal opioid medication were not allowed to be included in the UK. At Visit 2, all of the criteria mentioned above had to be met in order to enter the titration phase. At Visit 4, the subjects had a confirmed diagnosis of OIC, as determined by modified Rome III diagnostic criteria and BFI score ≥ 30 within the last seven days prior to randomisation (Visit 4), in order to enter the double-blind treatment phase. Adequate analgesia, i.e. decrease, no change; or increase of < 10 pixels on visual analogue scale (VAS) in mean pain intensity over the last seven days of the run-in phase (before Visit 4) compared to the mean of the last three days of the titration phase (before Visit 3) was required. The subjects had no more than one day with over two doses of opioid rescue medication per day during the last seven days before Visit 4 and no treatment-related intolerable adverse events (AEs) (according to the judgement of the investigator).	
Test products, dose and mode of administration, batch number:	Naloxone HCl PR tablets (NLX 6 mg, 12 mg, 24 mg, 48 mg), oral administration, once daily, TDD: 6-48 mg Batch number: 21102, 14010701, 21103, 14010703, 21104, 14012005, 21105, 14012003	

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Reference therapy, dose and mode of administration, batch number:	Corresponding placebo tablets (NLX PLA 3 mg [placebo run-in only], 6 mg, 12 mg, 24 mg, 48 mg), oral administration, once daily, TDD: 3-48 mg Batch number: 22503, 13101402, 22101, 14010205, 22406, 14010705, 22407, 14010707, 22110, 14010804
Non-investigational medicinal products, dose and mode of administration:	Trial opioids: • Oxycodone (Oxy) hydrochloride PR tablets XL (20 mg, 40 mg, 80 mg), oral administration, once daily, total daily dose: 20 mg, 40 mg, 60 mg or 80 mg • Hydromorphone (HyMo) hydrochloride PR tablets XL (8 mg, 16 mg, 32 mg), oral administration, once daily, total daily dose: 8 mg, 16 mg, 24 mg or 32 mg Opioid rescue medication: • Morphine sulphate 10 mg immediate-release tablets, oral administration, as needed, single dose: 5-20 mg, depending on trial opioid dose Laxative rescue medications: • Bisacodyl 5 mg gastro-resistant tablets, oral administration, single dose: 5-20 mg (1-4 tablets) • Bisacodyl 10 mg suppositories, rectal administration, single dose: 10 mg, one suppository
Duration of treatment:	The subjects were treated for two weeks during the placebo run-in phase, up to a maximum of 12 weeks (+/- 2 days) during the double-blind dose-escalation / treatment phase and up to a maximum of two weeks (+/- 2 days) during the double-blind extension phase. The maximum study duration including screening, titration and follow-up phase was 23 weeks.
Criteria for evaluation:	
Efficacy:	Primary: • Absolute change in BFI score at the end of Week 12 (Visit 11) compared to baseline (Visit 4)

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Secondary:

1. Relative change in BFI score at the end of Week 12 (Visit 11) compared to baseline (Visit 4)
2. Absolute and relative changes from weekly BFI score at baseline (Visit 4) to the mean BFI score of Week 9 ─ 12 of the double-blind dose-escalation / treatment phase
3. Absolute and relative changes from baseline (Visit 4) in BFI score at the end of each week (at each visit) during the double-blind dose-escalation / treatment phase and the extension phase
4. Proportion of subjects ('responders') with a decrease in BFI score of ≥ 12 as compared with baseline (Visit 4) at the end of Week 12 (Visit 11) of the double-blind dose-escalation / treatment phase
5. Number of weeks with a decrease in BFI score of ≥ 12 as compared with baseline (Visit 4) during the double-blind dose-escalation / treatment phase
6. Proportion of subjects ('additional responders') with a decrease in BFI score of ≥ 12 in ≥ 9 weeks out of the 12-week double-blind dose-escalation / treatment phase as compared with baseline (Visit 4)

AA-1. Absolute and relative changes from baseline (Visit 4) in BFI at each week by naloxone dose at the corresponding visit for the double-blind dose-escalation / treatment phase (additional analysis [AA])

AA-2. Absolute and relative changes from baseline (Visit 4) in BFI score at each week by opioid dose in the double-blind dose-escalation / treatment phase (additional analysis)

7. Absolute and relative changes from baseline (Visit 4) in mean numbers of BMs, SBMs, and CSBMs per week during the last four weeks (Week 9 to 12) of the double-blind dose-escalation / treatment phase

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8. Absolute and relative changes from baseline (Visit 4) in mean daily number of BMs, SBMs, and CSBMs at each week during the double-blind dose-escalation / treatment phase and the extension phase
9. Proportion of subjects with ≥ 3 CSBMs per week during the last four weeks (Week 9 to 12) of the double-blind dose-escalation / treatment phase
10. Number of weeks with ≥ 3 CSBMs during the double-blind dose-escalation / treatment phase and the extension phase
11. Number of weeks with an increase of at least 1 CSBM over baseline (Visit 4) during the double-blind dose-escalation / treatment phase and the extension phase

AA-3. Absolute and relative change from baseline (Visit 4) in standardised number of BMs, SBMs and CSBMs per week by week for the double-blind dose-escalation / treatment phase (additional analysis)

AA-4. Absolute and relative changes from baseline (Visit 4) in standardised number of CSBMs per week by week and by naloxone dose at the corresponding week for the double-blind dose-escalation / treatment phase (additional analysis)

AA-5. Absolute and relative changes from baseline (Visit 4) in standardised numbers of CSBMs per week by week and by opioid dose during the double-blind dose-escalation / treatment phase and extension phase (additional analysis)

AA-6. Proportion of subjects (responders I) with ≥ 3 CSBMs per week and an increase of ≥ 1 CSBM per week compared to baseline (Visit 4) by week during the double-blind dose-escalation / treatment phase (additional analysis)

AA-7. Proportion of subjects (responders II) with ≥ 3 CSBMs per week and an increase of ≥ 1 CSBM per week compared to baseline (Visit 4) based on an overall 75%

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response rate related to the total duration of the double-blind dose-escalation / treatment phase (additional analysis)

AA-8. Proportion of subjects (responders III) with ≥ 3 CSBMs per week and an increase of ≥ 1 CSBM per week compared to baseline (Visit 4) based on an overall 100% response rate for the last four weeks of treatment (Week 9 to 12) ('sustained response') (additional analysis)

AA-9. Proportion of subjects (responders IV) with ≥ 3 CSBMs per week and an increase of ≥ 1 CSBM per week compared to baseline (Visit 4) based on an overall 75% response rate, i.e. 9 out of 12 weeks related to the 12 week double-blind treatment phase and among them the last four weeks (Week 9 to 12) with an overall 100% response rate, i.e. in all four weeks (additional analysis)

12. Absolute and relative change from baseline (Visit 4) in proportion of type 1 and 2 defecations per week according to BSFS at the end of Week 12 (Visit 11)

13. Absolute and relative change from baseline (Visit 4) in each item of the Symptoms of Defecation Score to Week 12 (Visit 11)

14. Absolute and relative change from baseline (Visit 4) in PAC-SYM at the end of each 2-week escalation step as well as at the end of the double-blind dose-escalation / treatment phase and the extension phase

15. Absolute and relative change from baseline (Visit 4) in PAC-QOL at the end of each 2-week escalation step as well as at the end of the double-blind dose-escalation / treatment phase and the extension phase

16. Mean number of days with laxative rescue medication use per week during the single-blind Naloxone HCl PR Placebo run-in phase, the double-blind dose-escalation / treatment phase and the extension phase

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	17.	Percentage of days with laxative use during the single-blind Naloxone HCl PR Placebo run-in phase, the double-blind dose-escalation / treatment phase, and the extension phase
	18.	Differences in recurrence of OIC-related symptoms using BFI; number of BMs, SBMs, and CSBMs; BSFS, Symptoms of Defecation Score, PAC-SYM, PAC-QOL and laxative use between abrupt and tapered cessation of Naloxone HCl PR / Naloxone HCl PR Placebo during the extension phase
	19.	Correlation between opioid total daily dose (morphine equivalents) and individually determined final IMP dose at Week 12 of double-blind dose-escalation / treatment phase
Safety:	20.	Absolute and relative change from baseline (Visit 4) in mean weekly PI at each week during the double-blind dose-escalation / treatment phase and the extension phase
	21.	Mean number of opioid rescue doses per week during the single-blind Naloxone HCl PR Placebo run-in phase, the double-blind dose-escalation / treatment phase, and the extension phase
	22.	Mean daily dose of opioid rescue medication per week during the single-blind Naloxone HCl PR Placebo run-in phase, the double-blind dose-escalation / treatment phase, and the extension phase
	AA-10.	Numbers of opioid rescue medication doses (intakes) per week during the single-blind Naloxone HCl PR Placebo run-in phase, the double-blind dose-escalation / treatment phase, and the extension phase (additional analysis)
	AA-11.	Numbers of days with opioid rescue medication use per week during the single-blind Naloxone HCl PR Placebo run-in phase, the double-blind dose-escalation / treatment phase, and the extension phase (additional analysis)

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	23. Absolute and relative change from baseline (Visit 4) in opioid withdrawal symptoms assessed by the modified SOWS at the end of each 2-week escalation step as well as at the end of the double-blind dose-escalation / treatment phase and the extension phase 24. The rate of treatment failures at Visit 6 due to safety reasons including effect on PI 25. Standard physical examination 26. Clinical laboratory assessments 27. Vital Signs 28. Adverse Events Additionally for France according to Protocol Amendment No. 1 dated 10-MAY-2013: 29. Absolute and relative change from Visit 1 in signs orienting towards misuse, abuse or psychological dependence evaluated by the Current Opioid Misuse Measure (COMM) questionnaire at each in-house visit until the end of the extension phase
Statistical methods:	Analysis sets The Full Analysis Set (FAS) was defined as all subjects randomised to NLX or NLX PLA at Visit 4, who received at least one dose of the double-blind IMP, and with at least one post-baseline (i.e. after Visit 4) assessment of BFI during the double-blind dose-escalation / treatment phase. The Per-Protocol Set (PPS) was defined as all FAS-evaluable subjects who completed the double-blind treatment phase without major protocol violations that could have an influence on bowel function or bowel function assessment. The Safety Set was defined as all subjects randomised to NLX or NLX PLA at Visit 4 who received at least one dose of the double-blind IMP. Continuous data were summarised by using descriptive statistics -

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number of subjects, mean, standard deviation (SD), median and range (minimum and maximum). Categorical variables were summarised by using frequency (counts) and proportions (percent) of subjects with non-missing data per category.

Analysis of primary efficacy endpoint

The analysis of the primary efficacy endpoint and additional sensitivity analyses were performed according to the Global Protocol Amendment No. 2, dated 25-FEB-2015.

For the primary efficacy outcome measure, BFI absolute change between baseline (Visit 4) and the end of Week 12 (Visit 11) of the double-blind dose-escalation / treatment phase, a mixed model for repeated measurements (MMRM) approach was carried out using treatment, week, pooled centres, gender, opioid type (Oxy or HyMo) and opioid TDD (low-dose range; high-dose range) as fixed factors, and baseline BFI and standardised number of days with laxative rescue medication use per week during the run-in phase as continuous covariates. Centres with less than 10 subjects were pooled within country and centres from different countries were combined in the case that less than 10 subjects by country after pooling were reported.

The confirmatory analysis was performed in the FAS using a one-sided, trial-wise type I error rate of $\alpha = 0.025$ for the treatment effect.

In addition the primary efficacy endpoint was analysed on the PPS. The analysis of the PPS was intended to provide supportive evidence of the analysis of the FAS.

Sensitivity analysis of the primary variable was conducted using the analysis of covariance (ANCOVA) model with the factors and covariates that were used in the MMRM analysis. The last observation carried forward (LOCF) imputation approach for missing BFI values at Week 12 was applied. In addition, observed case (OC) data were analysed using the same ANCOVA model.

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Analysis of secondary efficacy endpoints

All secondary efficacy endpoints were analysed descriptively.

In addition to the planned primary efficacy endpoint analysis, CSBM responder proportions between treatment groups were analysed and interpreted exploratory using a logistic regression model (additional analysis) to assess the treatment effect. The model incorporated the same covariates as used in the MMRM model in the sensitivity analysis for the primary endpoint.

Secondary efficacy analyses were performed on the same analysis sets as for the primary endpoint.

The primary endpoint and (selected) secondary endpoints were analysed by subgroups. The MMRM model with treatment and week as fixed factors and baseline BFI as covariate was used for analysis of the primary endpoint in the subgroups.

By-subject data listings were prepared to support all statistical summary tables and for other electronic Case Report Form data, as appropriate.

Analysis of safety endpoints

The Safety Set 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, seriousness and drug-event relationship of TEAEs were summarised separately. All AEs were listed.

Vitals signs, pain intensity and subjective opioid withdrawal scale scores, including changes from baseline were summarised.

Number and percent of subjects with normal / abnormal physical examination results for each parameter were presented.

Frequency tables were presented for abnormal values of laboratory parameters.

Only for France: Current Opioid Misuse Measure (COMM) scores including changes from Visit 1 were summarised.

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SUMMARY OF RESULTS

EFFICACY RESULTS:

The primary objective of this study to demonstrate that administration of Naloxone hydrochloride (HCl) PR (prolonged-release) tablets (NLX) once daily is superior to Naloxone HCl PR Placebo (NLX PLA or placebo) in the improvement / reversal of opioid-induced constipation was missed:

- The primary endpoint, absolute change in **Bowel Function Index (BFI)** at the end of Week 12 compared to baseline, analysed using a MMRM model for the FAS population, showed a decrease of -26.73 points for the NLX group and a decrease of -21.76 points for the placebo group. The estimated least square mean difference between the treatment groups (-4.97 points, 95% confidence interval (CI) [-11.82, 1.87]) was not statistically significant (p = 0.1534).

  Statistically significant treatment differences in favour of the NLX group were reported in six weeks out of the 12-week dose-escalation / treatment phase (Week 1 and Week 5 to Week 9). The progression of changes in BFI in both treatment groups, as calculated in the MMRM analysis is depicted in the figure below.

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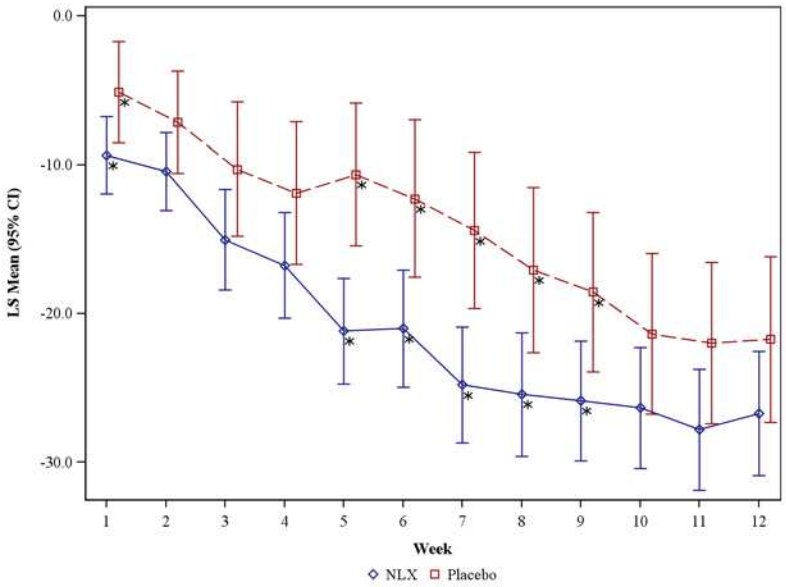

Source: Section 15.2, Figure 15.2.1 and Section 15.2, Table 15.2.1.1.1
CI: Confidence interval, LS: Least square
Note: Weeks with statistically significant treatment difference are marked with an asterisk.

- Both treatment groups showed a clinically meaningful BFI improvement, i.e. a reduction of ≥ 12 points at the end of Week 12 for both data sets (LOCF and OC data). More subjects in the NLX group (38.8%) presented a decrease in BFI score of ≥ 12 compared with baseline in nine or more weeks out of the 12-week treatment phase compared with the placebo group (33.9%).
- In both treatment groups changes from baseline to Week 9 to Week 12 (mean $BFI_{Week9-12}$) were very similar to the results seen at Week 12 indicating that the BFI remained stable during the last four weeks of constant dosing (LOCF and OC data).
- Results from the responder analysis of **complete spontaneous bowel movements (CSBMs)** were in line with the results on

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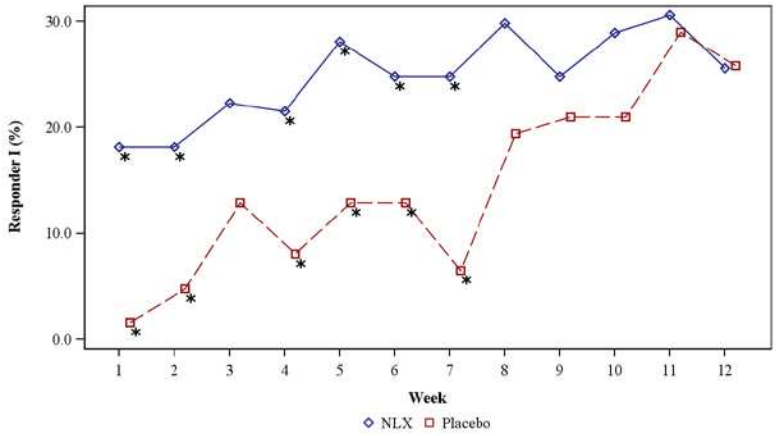
the BFI. CSBM response was defined as at least three CSBMs per week and an increase of at least one CSBM per week over baseline (Visit 4). From Week 1 to Week 11, the CSBM responder rates by week (CSBM responders I) were higher in the NLX group compared with the placebo group (range between 18.2% and 30.6% in the NLX group vs. 1.6% and 29.0% in the placebo group). At Week 12, similar CSBM responder rates were observed in the NLX group and in the placebo group (25.6% vs. 25.8%). The responder rates in the NLX group remained more or less on a stable level between Week 9 and Week 12, while the rates increased unexpectedly in the placebo group especially from Week 10 to Week 11 and Week 12. In six weeks out of the 12-week dose-escalation / treatment phase (Week 1 and 2 and from Week 4 to Week 7), adjusted odds ratios showed statistically significant treatment differences in favour of NLX compared to placebo. The progression of CSBM responder rates by week (CSBM responders I) is shown in the figure below.



Source: Section 15.2, Figure 15.2.3.5.1 and Section 15.2, Table 15.2.3.10.2.1
Note: Weeks with statistically significant treatment difference are marked with an asterisk.

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- The rate of CSBM responders II based on an overall 75% response rate (i.e. CSBM response in at least 9 of 12 weeks) revealed, with an adjusted odds ratio of 3.9 in favour of the NLX group, a statistically significant treatment difference ($p = 0.0449$, 95% CI [1.03, 15.11]). A treatment difference of more than 10% was reported with 19 (15.7%) NLX responders versus three (4.8%) placebo responders.
- In the CSBM responder III analysis, the 'sustained response' defined as fulfilling responder criteria for the last four weeks of treatment (Week 9 to 12), slightly higher rates were observed in the NLX group compared with the placebo group (14.0% vs. 11.3%). The adjusted odds ratio was 1.3 ($p = 0.6596$, 95% CI [0.43, 3.76]).
- Other CSBM analyses supported these outcomes. Mean absolute changes from baseline in standardised numbers of CSBMs per week at each week during the treatment phase revealed better results in the NLX group compared with the placebo group. Median absolute changes were identical or better in the NLX group up to Week 10. Only in the last two weeks higher changes from baseline were observed in the placebo group compared to the NLX group. Increases to median 1.40 CSBMs per week in the NLX group vs. median 1.91 CSBMs per week in the placebo group corresponding to median absolute changes from baseline of 0.17 CSBMs vs. 0.88 CSBMs, respectively, were observed in Week 12 (OC). During the last four weeks (Week 9 to 12) the NLX group showed better results compared with the placebo group with increases to a median of 1.7 CSBMs per week in the NLX group vs. 1.4 CSBMs per week in the placebo group, corresponding to median absolute changes from baseline of 0.7 CSBM vs. 0.5 CSBMs per week, respectively (OC data).

The improvement in BFI scores and CSBM responder analyses in NLX subjects was also reflected by a positive development of all other secondary efficacy endpoints (OC data):

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- The evaluation of the **Bristol Stool Form Scale (BSFS)** revealed a softer stool consistency at Week 12 compared to baseline. Absolute changes from baseline of more than 15.0% in BMs assigned to constipation (BSFS type 1-2 defecations) were reported from Week 4 to Week 12 in the NLX group whereas such changes were reported only for Weeks 11 and 12 in the placebo group (LOCF and OC data).
- The total **Symptoms of Defecation Score (SDS)** improved from baseline to Week 12 with more favourable results for NLX subjects regarding the absolute change from baseline compared to placebo subjects (mean 5.2 [SD: 3.74] vs. 4.4 [SD: 3.66], mean absolute change of -2.9 [SD: 3.64] vs. -2.5 [SD: 4.46], respectively).
- Global mean **Patient Assessment of Constipation - Symptoms scale (PAC-SYM)** score changed from 'mild to moderate symptoms' at baseline to 'absence of symptoms to mild symptoms' at Week 12 in both treatment groups.
- For the mean **Patient Assessment of Constipation - Quality of Life scale (PAC-QOL)** score, a mean decrease of 0.5 points was observed in both treatment groups corresponding to a clinically relevant improvement for the overall PAC-QOL score.
- The **laxative rescue medication use** showed a stronger decrease in the NLX group compared to the placebo group. The change in percentage of days per week between run-in and treatment phase decreased by 7.1% in the NLX group versus 0.9% in the placebo group (median change). In general, higher median absolute changes were reported for each week in the NLX group compared with the placebo group regarding the number of days per week with laxative rescue medication use.

<u>Dose escalation and optimal dose selection after Week 8</u>

During the dose escalation phase (Week 1 to Week 8), both treatment groups showed improving BFI values. Starting from

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Week 5 to Week 9, also the difference between the treatment groups increased persistently and was statistically significant in favour of the NLX group over the placebo group, indicating an increasing effect with increasing NLX dose. Analyses of the CSBM data corroborate this result.

The majority of the subjects in the NLX group escalated their dose to NLX 48 mg until the end of dose-escalation phase (82.6%, 100 subjects at Week 8) without safety concerns in terms of pain intensity, opioid rescue medication use and treatment-related intolerable AEs. At Week 9, after evaluating the optimal individual BFI result and safety concerns, the majority of subjects in the NLX group were assigned to NLX 48 mg (47.2%, 51 subjects) or NLX 24 mg (25.0%, 27 subjects) as their final dose. Only 30 subjects were allocated to NLX 12 mg (22.2%, 24 subjects) or NLX 6 mg (5.6%, six subjects).

Efficacy analyses after assignment to final dose (Week 9 onwards) revealed ambiguous results:

- BFI results showed that during the last four weeks, the mean absolute change from baseline increased with increasing NLX doses (range from approximately -21 points for NLX 6 mg to approximately -29 points for NLX 48 mg). When comparing absolute mean changes from baseline of NLX and placebo group, greater reductions were observed in the NLX group for each IMP dose except for IMP 48 mg with similar mean absolute changes in both treatment groups.
- CSBM responder I analyses confirmed this result. The average of CSBM response during the last four weeks in the NLX group was ~ 7.5% for NLX 6 mg, ~ 27% for NLX 12 mg, ~ 28% for NLX 24 mg and ~ 32% for NLX 48 mg. Placebo response however was high for placebo 48 mg (ranging from 34.6% to 46.2% during Week 9 to Week 12). This subgroup accounted for 42% of subjects on placebo during that phase of the study. Responder rates were notably higher (difference of > 10%) in the NLX group compared to the placebo group for

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IMP 24 mg (27.5% vs. 11.4%), and higher for IMP 12 mg (26.8% vs. 21.4%) and 6 mg (7.5% vs. 2.2%).

Subgroups

When treatment effects were analysed within subgroups (laxative pre-treatment, gender, opioid type and opioid TDD), treatment groups generally behaved similar to the overall population.

In the laxative pre-treatment subgroups, there were only four laxative pre-treatment partial responders in the NLX group and they were not analysed. Similar treatment effects regarding the BFI LS mean treatment difference at Week 12 were observed between laxative pre-treatment non-responders compared with laxative pre-treatment non-users. The subgroup-treatment interaction in BFI was found to be not statistically significant ($p = 0.5097$). In the sustained CSBM response (CSBM responder III) analysis a higher treatment difference was observed in the subgroup of laxative pre-treatment non-responders between NLX and placebo subjects (18.2% vs. 13.6%).

The subgroups regarding opioid TDD showed a higher treatment effect in the high opioid TDD group (> 80 mg morphine equivalent [ME]) compared with the low opioid TDD group (≤ 80 mg ME). However, the subgroup-treatment interaction in BFI was found to be not statistically significant ($p = 0.1340$). This higher treatment effect in the high opioid TDD group was confirmed in the sustained CSBM response (responder III) analysis.

Changes in BFI and CSBMs were also evaluated descriptively for each opioid TDD group (40 mg, 80 mg, 120 mg and 160 mg ME). Baseline BFI values for the four dose strengths showed notable differences and were in parallel with increasing opioid doses in the NLX group. The mean absolute changes from baseline did not correlate to increasing morphine equivalents in the NLX group at Week 12. At Week 12, the highest mean absolute change from baseline was observed for 120 mg ME (-37.20 points [SD: 21.05])

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	in the NLX group. Similar mean changes from baseline between -24.1 and -26.4 points were observed for the other three opioid ME doses. Within one ME dose group, for nearly all weeks from Week 1 to Week 8, higher mean absolute changes from baseline were observed in the NLX group compared with the placebo group. From Week 9 to Week 12, higher mean changes in the NLX group were reported for 40 mg ME and for 120 mg ME, and lower mean changes compared to the placebo group for 80 mg ME and 160 mg ME. With regard to CSBMs during Week 9 to Week 12, a clinically relevant increase of at least one CSBM per week (median absolute change) was reported for 40 mg ME in Week 11 and for 120 mg ME from Week 9 to Week 12. For 80 mg ME and 160 mg ME, median absolute changes of 0.00 CSBMs per week were observed from Week 9 to Week 12. In the placebo group an increase of at least one CSBM per week was observed for 40 mg ME at Weeks 11 and 12, and for 160 mg ME from Week 9 to Week 12. <u>Extension Phase:</u> Potential differences between abrupt and tapered cessation were evaluated for the primary and the secondary efficacy parameters. The two cessation methods were well comparable regarding recurrence of OIC-related symptoms.
SAFETY RESULTS:	The mean **treatment duration** in the treatment phase was comparable between the two treatment groups: 78.3 days (SD: 16.77) in the NLX and 81.4 days (SD: 11.97) in the placebo group. The average daily doses of IMP during the treatment phase were similar in both treatment groups: 23.5 mg (SD: 7.51) of NLX and 23.4 mg (SD: 7.58) of placebo. The proportion of subjects with any **treatment emergent adverse events (TEAEs)** was comparable between the treatment groups (60.3% of the NLX and 59.7% of the placebo group subjects). The most frequently affected primary SOCs were gastrointestinal disorders, infections and infestations, and nervous system

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disorders.

The most frequent individual TEAEs by Preferred Term (PT) in the NLX and the placebo group were headache (11.6% vs. 14.5%), abdominal distension (9.1% vs. 8.1%) and abdominal pain (8.3% vs. 6.5%). The incidence of abdominal pain and abdominal distension was slightly higher in the NLX group, whereas the incidence of headache, nausea and nasopharyngitis was lower in the NLX group compared to the placebo group.

The overall frequency of individual TEAEs considered as at least possibly related was low. The incidence of subjects with such TEAEs was higher in the NLX group (19.0%) compared to the placebo group (12.9%). The most common related TEAEs comparing the NLX group with the placebo group were abdominal pain (5.8% vs. 3.2%), abdominal distension (3.3% vs. 0.0%), flatulence and headache (2.5% vs. 0.0%, each).

The vast majority of any TEAEs were classified as mild or moderate in intensity, the overall frequency of severe TEAEs was low (NLX: 6.6%; placebo: 1.6%).

The frequency of serious TEAEs was low (five NLX group subjects in total). One NLX group subject died due to acute cardiac failure 11 days after the last IMP intake (NLX 6 mg at the end of tapered cessation). All serious TEAEs were assessed by the investigators as unrelated to IMP.

The frequency of any TEAEs leading to premature discontinuation was low and was similar in both treatment groups (four [3.3%] subjects in the NLX and two [3.2%] subjects in the placebo group experienced a total of seven TEAEs, each with another Preferred Term). Three of the seven TEAEs leading to premature discontinuation (constipation, abdominal discomfort and drug withdrawal syndrome), were assessed as being at least possibly related to IMP. They were reported only in the NLX group.

The proportion of subjects who experienced any TEAE leading to IMP dose reduction was similar in both treatment groups (NLX:

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4.1%, placebo: 4.8%). The most frequent TEAE leading to dose reduction was abdominal pain (two NLX subjects and one placebo subject). All TEAEs leading to IMP dose reduction were considered to be at least possibly related to IMP. Furthermore, NLX dose was interrupted for one (0.8%) NLX group subject.

The overall incidence of clinically significant abnormal **laboratory values** at screening, Visit 11 (or EDV) or Visit 14, was low (eight subjects in the NLX and three subjects in the placebo group had clinically significant haematology or biochemistry results, three NLX subjects reported clinically significant abnormal urine test findings).

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

The changes in **pain intensity** in both treatment groups were minimal at each week as compared to baseline, with no major differences between the treatment groups. The groups' mean and median pain intensities at each week were below 40 pixels on the VAS, which is considered desirable for chronic pain management. The upper 95% CI was below 40 pixels at each measurement in both treatment groups.

No major changes within each treatment group or differences between the treatment groups were observed with regard to the **opioid rescue medication use** during the run-in, treatment and extension phases of the trial. The changes of opioid rescue medication doses (intakes) per week were minimal at each week as compared to baseline. From baseline, a slight decrease of -0.7 doses (median absolute change) was observed in the NLX group and a slight increase of 0.1 doses (median absolute change) in the placebo group at Week 12 (Visit 11).

Mean and median scores of **modified SOWS** were below 11 at each measurement in both treatment groups, showing absence or mild opioid withdrawal complications. The upper 95% CI was below 11 points at each measurement in both treatment groups.

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	The proportions of subjects with total SOWS scores below 11 increased from 76.0% at baseline to 88.2% at Visit 11 (OC) in the NLX group and from 83.9% to 89.5% in the placebo group corresponding to a higher improvement rate in the NLX group (+ 12.2%) compared with the placebo group (+ 5.6%). NLX revealed no major safety concerns as evaluated by TEAEs, laboratory parameters, vital signs, physical examinations, pain intensity, opioid rescue medication use and modified SOWS scores.
CONCLUSION:	This study missed its primary objective to demonstrate that the administration of Naloxone hydrochloride (HCl) PR (prolonged-release) tablets (NLX) once daily is superior to Naloxone HCl PR Placebo (placebo) in the improvement / reversal of opioid-induced constipation. However, statistically significant treatment differences in favour of the NLX group were reported in six weeks out of the 12-week dose-escalation / treatment phase (Week 1 and Week 5 to Week 9) in terms of reduction of BFI score from baseline. NLX-treated subjects showed a greater reduction from baseline to the end of Week 12 in the bowel function index (BFI) score compared to placebo with a clinically meaningful BFI improvement of $\geq$ 12 points at the end of Week 12. During the 4-step, 8-week dose-escalation phase, the BFI scores revealed a continuous decrease with increasing NLX doses from 6 mg to 48 mg per day which is compatible with a linear dose-response relationship. During the last four weeks (Week 9 to Week 12), when subjects received a stable NLX dose (the dose which was associated with the lowest BFI during the preceding eight weeks), the BFI scores showed only slight changes. The results for other efficacy parameters are consistent with this conclusion. Only the median number of CSBMs and the corresponding median absolute changes from baseline in the NLX group were higher during the last four weeks compared with Week 12.

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Based on BFI scores during the dose escalation phase, NLX 48 mg followed by NLX 24 mg was the most effective dose for the vast majority of subjects. The BFI score reduction increased with increasing opioid dose levels except the highest dose level of 160 mg ME.

The findings in the BFI score are supported by responder analyses conducted for the number of Complete Spontaneous Bowel Movements (CSBMs). CSBM response was defined as at least three CSBMs per week and an increase of at least one CSBM per week over baseline (Visit 4).

CSBM responder rates per week (CSBM responders I) were remarkably higher in the NLX group compared with the placebo group from Week 1 to Week 10 and reached statistically significantly better results in six weeks out of the 12-week dose-escalation / treatment phase.

The rate of subjects (CSBM responders II) showing CSBM response in at least 9 of 12 weeks, revealed a statistically significant treatment difference ($p = 0.0449$, 95% CI [1.03, 15.11]) with an adjusted odds ratio of 3.9 in favour of the NLX group.

More subjects showed a ‘sustained response’, i.e. CSBM response in each of the last four weeks of the treatment phase (Week 9 to Week 12), in the NLX compared to the placebo group (14.0% vs. 11.3%).

Other secondary efficacy outcome measures, such as BSFS, SDS, PAC-SYM, PAC-QOL and laxative rescue medication use support the results obtained for the BFI score and the CSBMs.

NLX revealed no major safety concerns as evaluated by TEAEs, laboratory parameters, vital signs, physical examinations, pain intensity, opioid rescue medication use and modified SOWS scores.

The unexpected, large placebo effect regarding reduction in BFI

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	score will be further discussed in a meta-analysis in which the results of the present study 0177/DEV (once daily administration of IMP) will be combined with the results of a similarly designed second study 0176/DEV (twice daily administration of IMP).	
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