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:	
Name of active ingredient: Naloxone hydrochloride	Page:	

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 3 mg to 24 mg twice 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): Czech Republic: 11 centres; France: 4 centres, Germany: 16 centres; Hungary: 8 centres; Italy: 2 centres, Slovakia: 6 centres, Spain: 6 centres
Publication (reference):	None.
Studied period (years):	date of first enrolment: 12-MAR-2013 date of last subject completed: 19-AUG-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) twice 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 twice daily in comparison to Naloxone HCl PR Placebo in terms of: a. decreased BFI b. increased frequency in bowel movements (bowel movement [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 twice 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 twice daily for the treatment of OIC. 4. to assess the effect of Naloxone HCl PR tablets administered twice 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 reaffirm the safety of the starting dose of 6 mg naloxone HCl per day which was considered safe according to published literature. 6. to assess the safety and tolerability of Naloxone HCl PR tablets administered twice daily. 7. 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 twice daily compared to placebo. 8. to assess the lack of systemic effects of Naloxone HCl PR tablets in terms of opioid withdrawal symptoms. 9. 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 −6 to Week −5, Visit 1 to Visit 2). The open-label opioid **titration phase** also had a maximum duration of 2 weeks (Week −4 to Week −3, Visit 2 to Visit 3). At Visit 2, the subjects discontinued their previous opioid treatment. They were randomised (1:1) to either oxycodone (Oxy) or hydromorphone (HyMo) trial medication. 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 1.5 mg twice

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daily 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 NLX within 30 days before V1	No NLX	**NLX PLA**	**NLX or NLX PLA**	**If tapering off: NLX or NLX PLA**	No NLX
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:	298
	Failed screening:	64
	Drop-outs before randomisation:	61
	Randomised:	173
	Withdrawn during treatment phase:	26
	Completed the treatment phase:	147
	Analysed (safety):	173
	Analysed (efficacy):	172
	Of 173 subjects randomised 115 subjects belonged to the NLX group and 58 to the placebo group. 147 (85.0%) subjects completed the double-blind treatment phase of the trial: 97 (84.3%) subjects in the NLX group and 50 (86.2%) 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 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 per week when not taking laxatives for at least the last four weeks before Visit 1. The subjects had a documented history of chronic	

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	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. 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 3 mg, 6 mg, 12 mg, 24 mg), oral administration, twice daily, TDD: 6-48 mg Batch number: 22502, 13110703, 21102, 14010701, 21103, 14010703, 21104, 14012005

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Reference therapy, dose and mode of administration, batch number:	Corresponding placebo tablets (NLX PLA 1.5 mg [placebo run-in only], 3 mg, 6 mg, 12 mg, 24 mg), oral administration, twice daily, TDD: 3-48 mg Batch number: 22401, 22503, 13101402, 22101, 14010205, 22406, 14010705, 22407, 14010707
Non-investigational medicinal products, dose and mode of administration:	Trial opioids: • Oxycodone (Oxy) hydrochloride PR tablets (10 mg, 20 mg, 40 mg), oral administration, twice daily, total daily dose: 20, 40, 60 or 80 mg • Hydromorphone (HyMo) hydrochloride PR tablets (4 mg, 8 mg, 16 mg), oral administration, twice daily, total daily dose: 8, 16, 24 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 2 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 22 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)

Ph-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 (post-hoc [Ph])

Ph-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 (post-hoc)

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 Week 12) of the double-blind dose-escalation / treatment phase
8. Absolute and relative changes from baseline (Visit 4) in

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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 Week 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 one CSBM over baseline (Visit 4) during the double-blind dose-escalation / treatment phase and the extension phase

Ph-3. Absolute and relative changes from baseline (Visit 4) in standardised number of BMs, SBMs and CSBMs per week by week for the double-blind dose-escalation / treatment phase and the extension phase (post-hoc)

Ph-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 (post-hoc)

Ph-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 (post-hoc)

Ph-6. Proportion of subjects (CSMB 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 (post-hoc)

Ph-7. Proportion of subjects (CSBM 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% response rate related to the total duration of the double-blind dose-escalation / treatment phase (post-hoc)

Ph-8. Proportion of subjects (CSBM responders III) with

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≥ 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 Week 12) ('sustained response') (post-hoc)

Ph-9. Proportion of subjects (CSBM 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 Week 12) with an overall 100% response rate, i.e. in all four weeks (post-hoc)

12. Absolute and relative change from baseline 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 placebo run-in , the double-blind dose-escalation / treatment and the extension phase

17. Percentage of days with laxative use during the single-blind placebo run-in, the double-blind dose-escalation / treatment and the extension phase

18. Differences in recurrence of OIC-related symptoms using

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		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 and individually determined final naloxone 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
	23.	Absolute and relative change from baseline (Visit 4) in opioid withdrawal symptoms assessed by the modified Subjective Opioid Withdrawal Scale (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:	
	29.	Absolute and relative change from Visit 1 in signs orienting

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	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 trial medication, 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 trial medication. Continuous data were summarised by using descriptive statistics - number of subjects, mean, standard deviation (SD), median, and range (minimum and maximum). Categorical variables were summarised by using frequency (counts) and proportions (percents) of subjects with non-missing data per category. <u>Analysis of primary efficacy endpoint</u> 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, an analysis of covariance (ANCOVA) was carried out using treatment, centre, age (≤ 65 years; > 65 years), sex, opioid drug (Oxy or HyMo) and opioid TDD (low-dose range; high-dose range) as categorical factors, and baseline BFI and number of days with laxative rescue medication use during the last four weeks as continuous covariates. The confirmatory analysis was performed in the FAS using a one-

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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.

As post-hoc analysis, a Mixed Model for Repeated Measurements (MMRM) analysis with modified covariates structure including treatment, pooled centres, sex, opioid drug and opioid TDD as categorical factors and baseline BFI and laxative rescue medication use during run-in period as continuous covariates was performed as sensitivity analysis for the primary efficacy outcome measure.

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 (post-hoc 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 of the study.

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

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 and drug-event relationship of TEAEs were summarised separately. All AEs were listed.

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	Vitals signs, pain intensity and subjective opioid withdrawal scale, including changes from baseline were summarised. A frequency table was presented for abnormal values of laboratory parameters. Only for France: Current Opioid Misuse Measure (COMM) including changes from Visit 1 was summarised.
SUMMARY OF RESULTS	
EFFICACY RESULTS:	This study met its primary objective to demonstrate that administration of Naloxone hydrochloride (HCl) PR (prolonged-release) tablets (NLX) twice daily is superior to Naloxone HCl PR Placebo (NLX PLA or placebo) in the improvement / reversal of opioid-induced constipation: • The primary endpoint, absolute change in **Bowel Function Index (BFI)** at the end of Week 12 compared to baseline, analysed using an LOCF / ANCOVA model for the FAS population, showed a decrease of -28.18 points for the NLX group and a decrease of -21.53 points for the placebo group. The estimated least square mean difference between the treatment groups (-6.65 points, 95% confidence interval (CI) [-13.23, -0.06]) was statistically significant (p = 0.0478). • Post-hoc sensitivity analyses were conducted using more advanced methods for missing data handling (Mixed Model for Repeated Measurements, MMRM) while at the same time the covariate structure of the model was simplified and corrected in concordance with current guidelines. The resulting post-hoc MMRM analysis of BFI scores at Week 12 showed for the NLX group a decrease of -34.81 points and for the placebo group a decrease of -26.93 points, resulting in a statistically significant LS mean difference of -7.89 points between the treatment groups, 95% CI [-14.42, -1.35], p = 0.0183. This result was in good agreement with the raw mean absolute changes from baseline at Week 12 (NLX -34.3 points, placebo -26.5 points,

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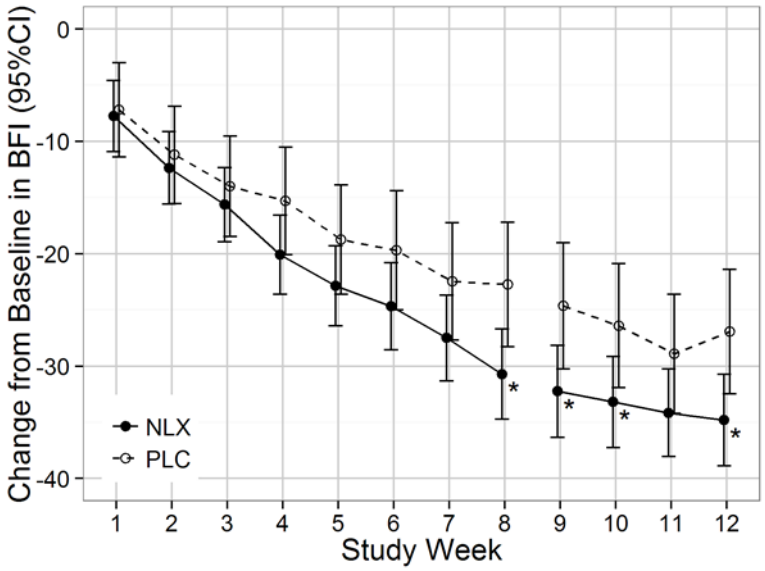
LOCF data). The progression of changes in BFI in both treatment groups, as calculated in this sensitivity analysis is depicted in the figure below.



Source: Section 15.2, post-hoc Figure P.15.2.2.4 and Table P.15.2.2.8.1
BFI: Bowel Function Index; CI: Confidence interval
* indicates statistically significant treatment difference at the respective week

- Both treatment groups showed a clinically meaningful BFI improvement of ≥ 12 points at the end of Week 12 but only in the NLX group the mean and median BFI score was lower than 30 points (corresponding to a normal / regular bowel function) for both data sets (LOCF and OC data). In line with this result, notably more subjects in the NLX group (59.6%) 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 (41.4%).
- In both treatment groups changes from baseline to Week 9 to Week 12 (mean $BFI_{Week9\text{-}12}$) were very similar to the results

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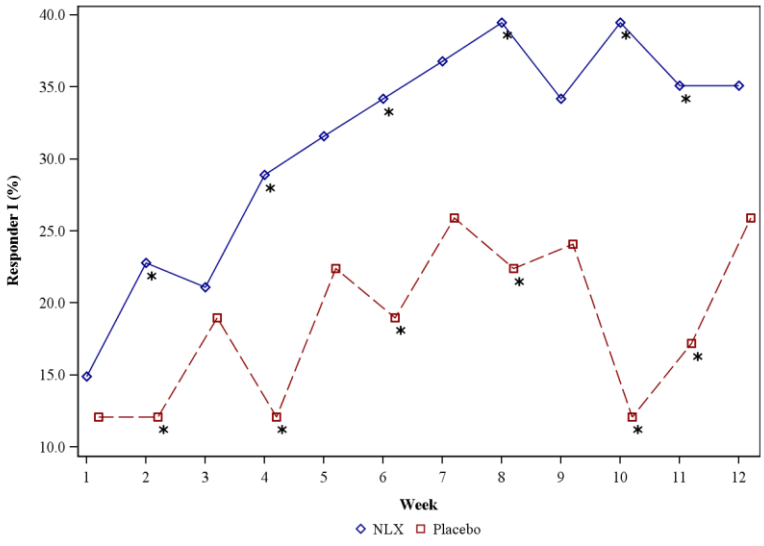
seen at Week 12, indicating that the BFI remained stable during the last four weeks of constant dosing (LOCF and OC data).

- Results from the responder analysis of **complete spontaneous bowel movements (CSBMs)** were in line with the results on 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). Throughout all 12 weeks of the treatment phase CSBM responder rates by week (CSBM responders I) were notably higher in the NLX group compared with the placebo group (at Week 12: 35.1% vs. 25.9%). In six weeks out of the 12-week dose-escalation / treatment phase (Week 2, Week 4, Week 6, Week 8, Week 10 and Week 11), 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, post-hoc Figure P.15.2.3.3.1 and Table P.15.2.3.10.2.1
* indicates statistically significant treatment difference at the respective week

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- In an important type of CSBM responder analyses (CSBM responders III), the 'sustained response' defined as fulfilling responder criteria for the last 4 weeks of treatment (Week 9 to Week 12), a statistically significant and clinically relevant difference of more than 10% was observed comparing the NLX group with the placebo group (25.4% vs. 10.3%, respectively). The adjusted odds ratio was 3.8 (95% CI [1.37, 10.54], p = 0.0102).
- Other CSBM analyses supported these positive 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. Increases to median 2.00 CSBMs per week were observed in Week 12 in the NLX group compared with median 0.79 CSBMs per week in the placebo group. Median absolute changes from baseline showed a clinically meaningful increase of 1.00 CSBM per week in the NLX group compared with 0.00 CSBMs per week in the placebo group. During the last four weeks (Week 9 to Week 12), a median absolute change of 1.0 CSBM per week from baseline to a median of 2.5 CSBMs per week was reported in the NLX group compared with a median absolute change of 0.0 CSBMs per week to a median of 0.8 CSBMs per week in the placebo group (OC data).

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

- The evaluation of the **Bristol Stool Form Scale (BSFS)** revealed a softer stool consistency at Week 12 compared to baseline. A total of 10.6% of the BMs in the NLX group versus 20.0% of the BMs in the placebo group were belonging to BSFS type 1-2 categories assigned to constipation (baseline 34.7% and 31.9%, respectively).
- The total **Symptoms of Defecation Score (SDS)** improved

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from baseline to Week 12 with more favourable results for NLX subjects compared to placebo subjects (mean 4.0 [SD: 2.90] vs. 5.3 [SD: 4.39], mean absolute change of -3.0 [SD: 3.64] vs. -2.0 [SD: 4.08], 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 decrease > 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 slightly 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 4.65% in the NLX group versus 0.00% in the placebo group (median change). At Week 12 a median decrease of 0.41 days per week corresponding to a decrease of 5.88% was observed in the NLX group compared with 0.11 days per week (1.54%) in the placebo group.

Dose escalation and optimal dose selection after Week 8

During the dose escalation phase (Week 1 to Week 8), both treatment groups showed constantly improving BFI values. Starting from Week 4, also the difference between the treatment groups increased persistently and 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 (78.1%, 89 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 optimal individual BFI result and safety concerns, the majority of subjects in the

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NLX group, were assigned to NLX 48 mg (47.6%, 49 subjects) or NLX 24 mg (25.2%, 26 subjects) as their final dose. Only 28 subjects were allocated to NLX 12 mg (17.5%, 18 subjects) or NLX 6 mg (9.7%, 10 subjects).

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

- BFI results showed that during the last 4 weeks, when comparing absolute mean changes from baseline of NLX and placebo group, notably greater reductions were observed in the NLX group for each IMP dose except for IMP 24 mg.
- CSBM responder I analyses confirmed this result. The average CSBM responder rates during the last four weeks in the NLX group were ~26% for NLX 12 mg, and around 30% to 40% for NLX 6 mg (~35%), 24 mg (~32%) and 48 mg (~43%). Placebo response however was unusually high and unstable for placebo 24 mg (ranging from 18.2% to 63.6% during Week 9 to Week 12). This subgroup accounted for 19% of subjects on placebo during that phase of the study. Placebo 6 mg and 12 mg groups showed placebo responses of 10% or lower, placebo 48 mg showed on average 22%.

<u>Subgroups</u>

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 subgroup, there were only three laxative pre-treatment partial responders per treatment group and those were not analysed. There was a clearly bigger BFI treatment effect in laxative pre-treatment non-responders compared with laxative pre-treatment non-users. Sustained CSBM response (CSBM responder III) analyses confirmed this result. The subgroup-treatment interaction in BFI was found to be not statistically significant ($p = 0.1981$).

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	The subgroups regarding opioid TDD showed clearly dissimilar treatment effects with the higher effect in the high opioid TDD group (>80 mg morphine equivalent [ME]). This result was confirmed in the sustained CSBM response (CSBM responder III) analysis. The subgroup-treatment interaction in BFI was statistically significant (p = 0.0183). Changes in BFI and CSBMs were also evaluated descriptively for each opioid TDD group (40 mg, 80 mg, 120 mg and 160 mg ME). The group of subjects with the lowest opioid TDD (40 mg ME, 43.6% of subjects of the total of both treatment groups) showed a markedly lower baseline BFI score compared to all other opioid TDD groups. As a result the treatment difference (OC) in BFI at Week 12 in this group was small. For 80 mg, 120 mg and 160 mg ME considerably higher mean absolute / relative changes from baseline were observed in the NLX group at Week 12 compared to the placebo group. In the NLX but not in the placebo group, the mean absolute changes from baseline showed continuous greater reductions in BFI score with increasing opioid TDD. With regard to CSBMs, the 40 and 80 mg ME opioid TDD groups showed the biggest placebo effect. Nonetheless, subjects in both low opioid TDD groups (40 mg ME and 80 mg ME) showed a clinically relevant increase of one or nearly one (median absolute change) in CSBMs per week during the last four weeks of treatment with NLX, while placebo subjects in the respective opioid TDD groups had an absolute median change of 0.00 CSBMs per week. <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** (treatment and extension phase) was similar in both treatment groups: 82.6 days (SD: 15.88) in the

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NLX and 81.3 days (SD: 19.85) in the placebo group. The average daily doses of IMP were comparable between the treatment groups: 22.5 mg (SD: 7.67) of NLX and 21.8 mg (SD: 7.75) of placebo.

The proportion of subjects with any **treatment emergent adverse events (TEAEs)** was higher in the NLX than in the placebo group (62.6% vs. 48.3%). The most frequently affected primary SOCs were infections and infestations, gastrointestinal disorders, nervous system disorders and musculoskeletal and connective tissue disorders.

The most frequent individual TEAEs by Preferred Term (PT) in the NLX and the placebo group were headache (13.0% vs. 13.8%) and nasopharyngitis (10.4% vs. 8.6%). Diarrhoea was reported only in the NLX group (nine subjects, 7.8%). The incidence of nausea and headache was similar in both treatment groups. The incidence of arthralgia and nasopharyngitis was slightly higher in the NLX group, whereas that of abdominal pain, dizziness, rhinorrhoea and increased lacrimation was higher in the placebo group.

The overall frequency of individual TEAEs considered as at least possibly related was low. The incidence of subjects with any TEAEs assessed as at least possibly related to IMP was higher in the NLX group (17.4%) compared with the placebo group (12.1%). The most common related TEAEs comparing the NLX group with the placebo group were diarrhoea (4.3% vs. 0%), abdominal pain (2.6% vs. 1.7%) and nausea (both 1.7%).

The vast majority of any TEAEs were classified as mild or moderate, the overall frequency of severe TEAEs was low (NLX: 5.2%; placebo: 1.7%).

No deaths were reported. The frequency of any serious TEAEs (TESAEs) was low, three NLX subjects experienced three TESAEs and one placebo subject experienced two TESAEs. All TESAEs were assessed by the investigators as unrelated to IMP.

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The frequency of any TEAEs leading to premature discontinuation was low and was similar in both treatment groups (five [4.3%] subjects in the NLX and three [5.2%] subjects in the placebo group). Nausea was the only individual TEAE leading to premature discontinuation of one subject in each treatment group. All other TEAEs leading to premature discontinuation were reported by one subject each. All TEAEs leading to premature discontinuation, except anxiety disorder (NLX) and testicular injury (placebo) were assessed as being at least possibly related to IMP.

The proportion of subjects who experienced any TEAEs leading to IMP dose reduction was higher in the NLX group than in the placebo group: nine (7.8%) subjects vs. one (1.7%) subject, respectively. The most frequent TEAEs leading to dose reduction were diarrhoea (four NLX subjects) and abdominal pain (two NLX and one placebo subject). All TEAEs leading to IMP dose reduction were considered to be at least possibly related to IMP. One of these TEAEs was unresolved (abdominal pain in the placebo group) and for one TEAE the outcome was unknown (back pain in one NLX subject). Except in three cases including one with unknown outcome and one with unknown TEAE onset, all TEAEs in the NLX group resolved within one day after dose de-escalation at the latest. The occurrence of these TEAEs leading to dose reduction was not strongly correlated with the NLX dose.

The overall incidence of clinically significant abnormal **laboratory values** was low and was higher in the NLX group (15 subjects with clinically significant haematology or biochemistry results, three subjects reported clinically significant abnormal urine test findings) than in the placebo group (two subjects with clinically significant biochemistry results).

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

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	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 VAS, which is considered desirable for chronic pain management. The upper 95% CI was below 40 pixels at each measurement in both treatment groups and the lowest upper 95% CIs were observed in the NLX group during the last four weeks where the subjects received a constant NLX dose. No major differences between the treatment groups were observed with regard to the mean number of **opioid rescue medication** doses per week as well as to the mean daily dose of opioid rescue medication per week during the run-in, treatment and extension phases of the trial. 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 and the lowest upper 95% CIs were observed in the NLX group during the last four weeks where the subjects received a constant NLX dose. The SOWS scores were lower in both groups during the treatment and extension phase compared with baseline. No major differences between the groups were observed. NLX revealed no 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 met its primary objective and demonstrated that the administration of Naloxone hydrochloride (HCl) PR (prolonged-release) tablets (NLX) twice daily is superior to Naloxone HCl PR Placebo (placebo) in the improvement / reversal of opioid-induced constipation. NLX-treated subjects showed a statistically significantly greater

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reduction from baseline to the end of Week 12 in the bowel function index (BFI) score compared to placebo.

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 remained more or less on a plateau. The results for other efficacy parameters are consistent with this conclusion.

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 improvement in BFI scores increased with increasing opioid dose in the NLX group, whereas no correlation between the decrease in BFI and opioid daily dose was seen in placebo subjects.

The positive 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 and reached statistically significantly better results in six weeks out of the 12 week dose-escalation / treatment phase.

Significantly 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 (25.4% vs. 10.3%).

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 safety concerns as evaluated by TEAEs,

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