



## Clinical trial results:

A randomised, double-blind, double-dummy, cross-over multicenter study to demonstrate equivalence in analgesic efficacy and bowel function taking oxycodone equivalents of 120 and 160 mg per day as achieved with the higher OXN PR tablet strengths (OXN60/30 mg PR, OXN80/40 mg PR) twice daily compared to the identical daily dose taken as a combination of lower tablet strengths in subjects with non-malignant or malignant pain that requires around-the-clock opioid therapy.

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-004888-31 |
| Trial protocol           | GB CZ IT ES    |
| Global end of trial date | 26 July 2016   |

### Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 11 August 2017  |
| First version publication date | 11 March 2017   |
| Version creation reason        | • New data added to full data set<br>Extension Phase is completed |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | OXN3508 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02321397 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Mundipharma Research GmbH & Co. KG   |
| Sponsor organisation address | Höhenstraße 10, Limburg, Germany, D-65549  |
| Public contact               | European Medical Operations, Mundipharma Research GmbH & Co KG, +44 1223424900, info@contact-clinical-trials.com |
| Scientific contact           | European Medical Operations, Mundipharma Research GmbH & Co KG, +44 1223424900, info@contact-clinical-trials.com |

Notes:

### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No                                | No |

Notes:

**Results analysis stage**

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 22 February 2016 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 22 February 2016 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 26 July 2016     |
| Was the trial ended prematurely?                     | No               |

Notes:

**General information about the trial**

Main objective of the trial:

Primary objective:

To demonstrate equivalence between multiple lower strength OXN PR tablets and a single higher strength OXN PR tablet taken at the same overall total daily dose as shown by:

- Analgesic efficacy based on the mean of subjects' 'Average Pain over the last 24 hours' at the last 2 visits of each Cross-over Period, as assessed by the Pain Intensity Scale.

Co-primary objective:

- Equivalent bowel function as assessed by the Bowel Function Index (BFI).

Protection of trial subjects:

Protection of trial subjects:

1) Inclusion criteria:

- Male or female subjects at least 18 years (females less than one year post-menopausal had to have a negative serum or urine pregnancy test prior to the first dose of study treatment, be non-lactating, and willing to use adequate and highly effective methods of contraception throughout the study. A highly effective method of birth control was defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as sterilisation, implants, injectables, combined oral contraceptives, some IUDs (Intrauterine Device, hormonal), sexual abstinence or vasectomised partner).

- Subjects had to be willing and able (e.g. mental and physical condition) to participate in all aspects of the study, including use of medication, completion of subjective evaluations, attending scheduled clinic visits, completing telephone contacts, and compliance with protocol requirements as evidenced by providing written, informed consent.

2) Exclusion criteria:

- Several exclusion criteria excluded subjects who were at risk from the use of IMP (e.g. those with hypersensitivity) or the study methods (please refer to protocol)

3) Dose discontinuation:

The Investigator(s) or subjects themselves were able to stop study treatment at any time for safety or personal reasons.

Investigators were to discontinue a subject from study treatment if the subject demonstrated opioid withdrawal, had an SAE due to an opioid withdrawal syndrome, had Markedly Abnormal Laboratory values or abnormal vital signs or vigilance impairment fulfilling at least one SAE criterion, or required more than 160/80 mg OXN per day.

4) Safety assessments consisted of monitoring and recording all AEs and SAEs, observed or volunteered, regardless of suspected causal relationship to the IMP. This included reactions, interactions, accidents, illnesses, misuse, abuse, lab values, vital signs, ECG, vigilance and SOWS.

Background therapy:

Rescue medication: Oxycodone immediate release capsules. Analgesic rescue medication may have been dosed no sooner than every 4 hours as needed. 6 analgesic rescue doses were the total maximum amount of analgesic rescue medication per day (on single occasions).

The analgesic rescue medication dose was approximately 1/6th the total daily maintenance dose. For a subject stabilised on OXN60/30 mg PR twice daily (HST or LST), the rescue dose of OxyIR would have been 20 mg; for a subject stabilised on OXN80/40 mg PR twice daily (HST or LST), the rescue dose of OxyIR would have been 25 mg.

Subjects, who consistently (i.e.  $\geq 3$  days per week) required more than 2 rescue doses per day of OxyIR were discontinued.

|   |                                       |
|---|---------------------------------------|
| Evidence for comparator: -                                |                                       |
| Actual start date of recruitment                          | 27 November 2014                      |
| Long term follow-up planned                               | Yes                                   |
| Long term follow-up rationale                             | Safety, Efficacy, Scientific research |
| Long term follow-up duration                              | 6 Months                              |
| Independent data monitoring committee (IDMC) involvement? | No                                    |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 25         |
| Country: Number of subjects enrolled | Spain: 23          |
| Country: Number of subjects enrolled | United Kingdom: 8  |
| Country: Number of subjects enrolled | Czech Republic: 70 |
| Country: Number of subjects enrolled | Germany: 86        |
| Country: Number of subjects enrolled | Italy: 5           |
| Worldwide total number of subjects   | 217                |
| EEA total number of subjects         | 217                |

Notes:

### Subjects enrolled per age group

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 149 |
| From 65 to 84 years                       | 65  |
| 85 years and over                         | 3   |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted a total of 40 sites in 6 countries (8 sites in the Czech Republic, 15 in Germany, 4 in Italy, 4 in Poland, 4 in Spain, 5 in the United Kingdom). In addition, 16 sites did not recruit subjects (1 in the Czech Republic, 2 in Germany, 5 in Spain, 5 in the UK, 1 in Italy and 2 in Poland).

### Pre-assignment

Screening details:

Screening period: up to 2 weeks, Run-in Phase: 1-4 weeks. Subjects who did not comply with all screening inclusion and exclusion criteria or withdrew their consent prior to entering the Run-In Period were considered Screening Failures. The Run-In Period served to qualify the subject for entry into the Double-blind Phase.

### Pre-assignment period milestones

|  |                    |
|--|--------------------|
| Number of subjects started                 | 217                |
| Intermediate milestone: Number of subjects | Run-in Period: 195 |
| Number of subjects completed               | 155 <sup>[1]</sup> |

### Pre-assignment subject non-completion reasons

|                            |  |
|----------------------------|--|
| Reason: Number of subjects | Screening failure: 22                                  |
| Reason: Number of subjects | Adverse event, non-fatal: 17                           |
| Reason: Number of subjects | Consent withdrawn by subject: 3                        |
| Reason: Number of subjects | Did not meet Double-blind Phase inclusion criteria: 16 |
| Reason: Number of subjects | Lack of therapeutic effect: 4                          |

Notes:

[1] - The number of subjects reported to be in the pre-assignment period is not consistent with the number starting period 1. It is expected that the number completing the pre-assignment period are also present in the arms in period 1.

Justification: This study was done in a cross-over design. Subjects received both, low and high strength tablets within their respective dosing group.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Double-blind Period   |
| Is this the baseline period? | Yes   |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

### Arms

|                              |                 |
|------------------------------|-----------------|
| Are arms mutually exclusive? | No              |
| <b>Arm title</b>             | OXN80/40 PR LST |

Arm description:

Subjects who received OXN Low Strength Tablet on a dose level of 80 mg oxycodone and 40 mg naloxone.

|  |  |
|--|--|
| Arm type                               | Active comparator                                |
| Investigational medicinal product name | Oxycodone/naloxone 80/40 mg low strength tablets |
| Investigational medicinal product code | OXN80/40 LST                                     |
| Other name                             |  |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use   |

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**Dosage and administration details:**

2x 40/20 mg oxycodone/naloxone combination twice daily. Total daily dose: 160mg/80mg oxycodone/naloxone

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | OXN80/40 PR HST |
|------------------|-----------------|

**Arm description:**

Subjects who received OXN High Strength Tablet on a dose level of 80 mg oxycodone and 40 mg naloxone.

|  |   |
|--|---|
| Arm type                               | Experimental                                      |
| Investigational medicinal product name | Oxycodone/naloxone 80/40 mg high strength tablets |
| Investigational medicinal product code | OXN80/40 HST                                      |
| Other name                             |   |
| Pharmaceutical forms                   | Tablet  |
| Routes of administration               | Oral use  |

**Dosage and administration details:**

80/40 mg oxycodone/naloxone combination twice daily. Total daily dose: 160mg/80mg oxycodone/naloxone

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | OXN60/30 PR LST |
|------------------|-----------------|

**Arm description:**

Subjects who received OXN Low Strength Tablet on a dose level of 60 mg oxycodone and 30 mg naloxone.

|  |  |
|--|--|
| Arm type                               | Active comparator                                |
| Investigational medicinal product name | Oxycodone/naloxone 60/30 mg low strength tablets |
| Investigational medicinal product code | OXN60/30 LST                                     |
| Other name                             |  |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use   |

**Dosage and administration details:**

20/10 and 40/20 mg oxycodone/naloxone combination twice daily. Total daily dose: 120mg/60mg oxycodone/naloxone

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | OXN60/30 PR HST |
|------------------|-----------------|

**Arm description:**

Subjects who received OXN High Strength Tablet on a dose level of 60 mg oxycodone and 30 mg naloxone.

|  |   |
|--|---|
| Arm type                               | Experimental                                      |
| Investigational medicinal product name | Oxycodone/naloxone 60/30 mg high strength tablets |
| Investigational medicinal product code | OXN60/30 HST                                      |
| Other name                             |   |
| Pharmaceutical forms                   | Tablet  |
| Routes of administration               | Oral use  |

**Dosage and administration details:**

60/30 mg oxycodone/naloxone combination twice daily. Total daily dose: 120mg/60mg oxycodone/naloxone

| Number of subjects in period 1 | OXN80/40 PR LST   | OXN80/40 PR HST   | OXN60/30 PR LST   |
|--------------------------------|-------------------|-------------------|-------------------|
| Started                        | 79                | 76                | 75                |
| Interim analysis               | 20 <sup>[2]</sup> | 20 <sup>[3]</sup> | 20 <sup>[4]</sup> |
| Completed                      | 75                | 73                | 72                |
| Not completed                  | 4                 | 3                 | 3                 |
| Adverse event, serious fatal   | 1                 | -                 | -                 |
| Consent withdrawn by subject   | -                 | 2                 | 1                 |
| Adverse event, non-fatal       | 2                 | -                 | 2                 |
| Lack of efficacy               | 1                 | 1                 | -                 |

| Number of subjects in period 1 | OXN60/30 PR HST   |
|--------------------------------|-------------------|
| Started                        | 73                |
| Interim analysis               | 20 <sup>[5]</sup> |
| Completed                      | 73                |
| Not completed                  | 0                 |
| Adverse event, serious fatal   | -                 |
| Consent withdrawn by subject   | -                 |
| Adverse event, non-fatal       | -                 |
| Lack of efficacy               | -                 |

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The interim analysis was only done with a fraction of the subjects who took part in the study.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The interim analysis was only done with a fraction of the subjects who took part in the study.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The interim analysis was only done with a fraction of the subjects who took part in the study.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The interim analysis was only done with a fraction of the subjects who took part in the study.

## Period 2

|                              |                 |
|------------------------------|-----------------|
| Period 2 title               | Extension Phase |
| Is this the baseline period? | No              |
| Allocation method            | Not applicable  |
| Blinding used                | Not blinded     |

Blinding implementation details:

No blinding. Subjects who had completed the Double-blind Phase had the option to receive open-label OXN PR HST for up to 24 additional weeks.

## Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | OXN160/80 mg PR HST |
|------------------|---------------------|

### Arm description:

Subjects who received OXN 80/40 mg tablets twice daily

|  |   |
|--|---|
| Arm type                               | Experimental                                      |
| Investigational medicinal product name | Oxycodone/naloxone 80/40 mg high strength tablets |
| Investigational medicinal product code | OXN80/40 HST                                      |
| Other name                             |   |
| Pharmaceutical forms                   | Tablet  |
| Routes of administration               | Oral use  |

### Dosage and administration details:

80/40 mg oxycodone/naloxone combination twice daily. Total daily dose: 160mg/80mg oxycodone/naloxone

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | OXN140/70 mg PR HST |
|------------------|---------------------|

### Arm description:

Subjects who received one OXN 80/40 mg tablet and one OXN 60/30 mg tablet per day.

|  |   |
|--|---|
| Arm type                               | Experimental                                      |
| Investigational medicinal product name | Oxycodone/naloxone 80/40 mg high strength tablets |
| Investigational medicinal product code | OXN80/40 HST                                      |
| Other name                             |   |
| Pharmaceutical forms                   | Tablet  |
| Routes of administration               | Oral use  |

### Dosage and administration details:

80/40 mg oxycodone/naloxone combination twice daily. Asymmetrical dosing of one OXN 80/40 mg tablet and one OXN 60/30 mg tablet per day. Total daily dose: 140mg/70mg oxycodone/naloxone

|  |   |
|--|---|
| Investigational medicinal product name | Oxycodone/naloxone 60/30 mg high strength tablets |
| Investigational medicinal product code | OXN60/30 HST                                      |
| Other name                             |   |
| Pharmaceutical forms                   | Tablet  |
| Routes of administration               | Oral use  |

### Dosage and administration details:

80/40 mg oxycodone/naloxone combination twice daily. Asymmetrical dosing of one OXN 80/40 mg tablet and one OXN 60/30 mg tablet per day. Total daily dose: 140mg/70mg oxycodone/naloxone

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | OXN120/60 mg PR HST |
|------------------|---------------------|

### Arm description:

Subjects who received OXN 60/30 mg tablets twice daily.

|  |   |
|--|---|
| Arm type                               | Experimental                                      |
| Investigational medicinal product name | Oxycodone/naloxone 60/30 mg high strength tablets |
| Investigational medicinal product code | OXN60/30 HST                                      |
| Other name                             |   |
| Pharmaceutical forms                   | Tablet  |
| Routes of administration               | Oral use  |

### Dosage and administration details:

60/30 mg oxycodone/naloxone combination twice daily. Total daily dose: 120mg/60mg oxycodone/naloxone

| <b>Number of subjects in period 2</b>               | <b>OXN160/80 mg PR<br/>HST</b> | <b>OXN140/70 mg PR<br/>HST</b> | <b>OXN120/60 mg PR<br/>HST</b> |
|---|--------------------------------|--------------------------------|--------------------------------|
| Started   | 70                             | 2                              | 66                             |
| Completed   | 65                             | 2                              | 61                             |
| Not completed                                       | 5                              | 0                              | 5                              |
| Adverse event, serious fatal                        | 1                              | -                              | -                              |
| Consent withdrawn by subject                        | 1                              | -                              | 2                              |
| Administrative (unable to attend<br>planned visits) | -                              | -                              | 1                              |
| Adverse event, non-fatal                            | -                              | -                              | 2                              |
| Lost to follow-up                                   | 1                              | -                              | -                              |
| Lack of efficacy                                    | 1                              | -                              | -                              |
| Protocol deviation                                  | 1                              | -                              | -                              |



## Baseline characteristics

### Reporting groups<sup>[1]</sup>

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | OXN80/40 PR LST |
|-----------------------|-----------------|

Reporting group description:

Subjects who received OXN Low Strength Tablet on a dose level of 80 mg oxycodone and 40 mg naloxone.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | OXN80/40 PR HST |
|-----------------------|-----------------|

Reporting group description:

Subjects who received OXN High Strength Tablet on a dose level of 80 mg oxycodone and 40 mg naloxone.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | OXN60/30 PR LST |
|-----------------------|-----------------|

Reporting group description:

Subjects who received OXN Low Strength Tablet on a dose level of 60 mg oxycodone and 30 mg naloxone.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | OXN60/30 PR HST |
|-----------------------|-----------------|

Reporting group description:

Subjects who received OXN High Strength Tablet on a dose level of 60 mg oxycodone and 30 mg naloxone.

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: Basline period started after Screening and Run-In

| Reporting group values  | OXN80/40 PR LST | OXN80/40 PR HST | OXN60/30 PR LST |
|---|-----------------|-----------------|-----------------|
| Number of subjects  | 79              | 76              | 75              |
| Age categorical<br>Units: Subjects  |                 |                 |                 |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                 |                 |                 |
| Age continuous<br>Units: years  |                 |                 |                 |
| arithmetic mean   | 56.7            | 56.7            | 56.9            |
| standard deviation  | ± 10.7          | ± 10.78         | ± 11.62         |
| Gender categorical<br>Units: Subjects   |                 |                 |                 |
| Female  | 38              | 38              | 44              |
| Male  | 41              | 38              | 31              |

| Reporting group values             | OXN60/30 PR HST | Total |  |
|------------------------------------|-----------------|-------|--|
| Number of subjects                 | 73              | 155   |  |
| Age categorical<br>Units: Subjects |                 |       |  |
| In utero                           |                 |       |  |

|  |                 |    |  |
|--|-----------------|----|--|
| Preterm newborn infants<br>(gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                 |    |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation  | 56.8<br>± 11.76 | -  |  |
| Gender categorical<br>Units: Subjects  |                 |    |  |
| Female   | 44              | 83 |  |
| Male   | 29              | 72 |  |

## End points

### End points reporting groups

|   |                     |
|---|---------------------|
| Reporting group title   | OXN80/40 PR LST     |
| Reporting group description:<br>Subjects who received OXN Low Strength Tablet on a dose level of 80 mg oxycodone and 40 mg naloxone.  |                     |
| Reporting group title   | OXN80/40 PR HST     |
| Reporting group description:<br>Subjects who received OXN High Strength Tablet on a dose level of 80 mg oxycodone and 40 mg naloxone. |                     |
| Reporting group title   | OXN60/30 PR LST     |
| Reporting group description:<br>Subjects who received OXN Low Strength Tablet on a dose level of 60 mg oxycodone and 30 mg naloxone.  |                     |
| Reporting group title   | OXN60/30 PR HST     |
| Reporting group description:<br>Subjects who received OXN High Strength Tablet on a dose level of 60 mg oxycodone and 30 mg naloxone. |                     |
| Reporting group title   | OXN160/80 mg PR HST |
| Reporting group description:<br>Subjects who received OXN 80/40 mg tablets twice daily  |                     |
| Reporting group title   | OXN140/70 mg PR HST |
| Reporting group description:<br>Subjects who received one OXN 80/40 mg tablet and one OXN 60/30 mg tablet per day.                    |                     |
| Reporting group title   | OXN120/60 mg PR HST |
| Reporting group description:<br>Subjects who received OXN 60/30 mg tablets twice daily.   |                     |
| Subject analysis set title  | OXN80/40 LST PPP    |
| Subject analysis set type   | Per protocol        |
| Subject analysis set description:<br>Per Protocol Population OXN80/40 LST treatment group   |                     |
| Subject analysis set title  | OXN80/40 HST PPP    |
| Subject analysis set type   | Per protocol        |
| Subject analysis set description:<br>Per Protocol Population OXN80/40 HST treatment group   |                     |
| Subject analysis set title  | OXN60/30 HST PPP    |
| Subject analysis set type   | Per protocol        |
| Subject analysis set description:<br>Per Protocol Population OXN60/30 HST treatment group   |                     |
| Subject analysis set title  | OXN60/30 LST PPP    |
| Subject analysis set type   | Per protocol        |
| Subject analysis set description:<br>Per Protocol Population OXN60/30 LST treatment group   |                     |
| Subject analysis set title  | Total PPP           |
| Subject analysis set type   | Per protocol        |
| Subject analysis set description:<br>Total per protocol population  |                     |
| Subject analysis set title  | OXN80/40 LST FAP    |
| Subject analysis set type   | Full analysis       |
| Subject analysis set description:<br>Full Analysis Population OXN80/40 LST treatment group  |                     |

|   |  |
|---|--|
| Subject analysis set title  | OXN80/40 HST FAP                                   |
| Subject analysis set type   | Full analysis                                      |
| Subject analysis set description:   |  |
| Full Analysis Population OXN80/40 HST treatment group   |  |
| Subject analysis set title  | OXN60/30 HST FAP                                   |
| Subject analysis set type   | Full analysis                                      |
| Subject analysis set description:   |  |
| Full Analysis Population OXN60/30 HST treatment group   |  |
| Subject analysis set title  | OXN60/30 LST FAP                                   |
| Subject analysis set type   | Full analysis                                      |
| Subject analysis set description:   |  |
| Full Analysis Population OXN60/30 LST treatment group   |  |
| Subject analysis set title  | Total FAP  |
| Subject analysis set type   | Full analysis                                      |
| Subject analysis set description:   |  |
| Full Analysis Population total  |  |
| Subject analysis set title  | OXN80/40 LST Interim                               |
| Subject analysis set type   | Sub-group analysis                                 |
| Subject analysis set description:   |  |
| Subjects receiving OXN80/40 LST in the interim analysis   |  |
| Subject analysis set title  | OXN80/40 HST Interim                               |
| Subject analysis set type   | Sub-group analysis                                 |
| Subject analysis set description:   |  |
| Subjects receiving OXN80/40 HST in the interim analysis   |  |
| Subject analysis set title  | OXN60/30 HST Interim                               |
| Subject analysis set type   | Sub-group analysis                                 |
| Subject analysis set description:   |  |
| Subjects receiving OXN60/30 HST in the interim analysis   |  |
| Subject analysis set title  | OXN60/30 LST Interim                               |
| Subject analysis set type   | Sub-group analysis                                 |
| Subject analysis set description:   |  |
| Subjects receiving OXN60/30 LST in the interim analysis   |  |
| Subject analysis set title  | Interim total                                      |
| Subject analysis set type   | Sub-group analysis                                 |
| Subject analysis set description:   |  |
| Total number of subjects in the interim analysis  |  |
| Subject analysis set title  | All LST PPP  |
| Subject analysis set type   | Per protocol                                       |
| Subject analysis set description:   |  |
| All subjects receiving LST tablets (OXN80/40mg and OXN60/30mg)  |  |
| Subject analysis set title  | All HST PPP  |
| Subject analysis set type   | Per protocol                                       |
| Subject analysis set description:   |  |
| All subjects receiving HST tablets (OXN80/40mg and OXN60/30mg)  |  |
| Subject analysis set title  | Total Exposure Safety Population (Extension Phase) |
| Subject analysis set type   | Full analysis                                      |
| Subject analysis set description:   |  |
| <p>The Total Exposure Safety Population was defined as subjects who received at least one dose of OXN PR HST in the Extension Phase and had at least one safety assessment after the first of such doses.</p> <p>Any patients who had a chance to report an AE (i.e., who attended a study visit) was considered to have had a safety assessment regardless of whether they have reported an AE or not.</p> <p>Subjects in the Total Exposure Safety Population were analysed 'as treated'.</p> |  |

**Primary: Analgesic efficacy based on the mean of subjects' 'Average Pain over the last 24 hours' at the last 2 visits of each Cross-over Period, as assessed by the Pain Intensity Scale**

|                 |   |
|-----------------|---|
| End point title | Analgesic efficacy based on the mean of subjects' 'Average Pain over the last 24 hours' at the last 2 visits of each Cross-over Period, as assessed by the Pain Intensity Scale |
|-----------------|---|

End point description:

Pain Intensity Scale (Numeric Rating Scale (NRS) 0 – 10) – 'Average Pain over the last 24 hours', as assessed at Visits 5 and 6 and at Visits 8 and 9, respectively.

The Primary analysis was done in the Interim Analysis. As the interim analysis already successfully proved equivalence in the average pain over the last 24 hours the analyses with the PPP and FAP were assumed to be descriptive.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

3 weeks, assessed after 2 and 3 weeks.

| End point values                     | OXN80/40 LST<br>PPP  | OXN80/40 HST<br>PPP  | OXN60/30 HST<br>PPP  | OXN60/30 LST<br>PPP  |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 49 <sup>[1]</sup>    | 49 <sup>[2]</sup>    | 48 <sup>[3]</sup>    | 48 <sup>[4]</sup>    |
| Units: Mean NRS over last 24 hours   |                      |                      |                      |                      |
| arithmetic mean (standard deviation) |                      |                      |                      |                      |
| Week 2 (Visit 5 or 8)                | 3.49 (± 1.043)       | 3.61 (± 1.397)       | 3.02 (± 1.082)       | 3.31 (± 1.24)        |
| Week 3 (Visit 6 or 9)                | 3.43 (± 1.118)       | 3.36 (± 1.253)       | 3.27 (± 1.106)       | 3.23 (± 1.077)       |

Notes:

[1] - Excluding subjects from the interim analysis

[2] - Excluding subjects from the interim analysis

[3] - Excluding subjects from the interim analysis

[4] - Excluding subjects from the interim analysis

| End point values                     | Total PPP            | OXN80/40 LST<br>Interim | OXN80/40 HST<br>Interim | OXN60/30 HST<br>Interim |
|--------------------------------------|----------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Subject analysis set | Subject analysis set    | Subject analysis set    | Subject analysis set    |
| Number of subjects analysed          | 97 <sup>[5]</sup>    | 20                      | 20                      | 20                      |
| Units: Mean NRS over last 24 hours   |                      |                         |                         |                         |
| arithmetic mean (standard deviation) |                      |                         |                         |                         |
| Week 2 (Visit 5 or 8)                | 3.36 (± 1.115)       | 3.5 (± 1.32)            | 3.3 (± 1.3)             | 3.3 (± 0.73)            |
| Week 3 (Visit 6 or 9)                | 3.39 (± 1.073)       | 3.5 (± 1.23)            | 3.5 (± 1.15)            | 3.4 (± 1.1)             |

Notes:

[5] - Excluding subjects from the interim analysis

| End point values                     | OXN60/30 LST<br>Interim | Interim total        |  |  |
|--------------------------------------|-------------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set    | Subject analysis set |  |  |
| Number of subjects analysed          | 20                      | 40                   |  |  |
| Units: Mean NRS over last 24 hours   |                         |                      |  |  |
| arithmetic mean (standard deviation) |                         |                      |  |  |
| Week 2 (Visit 5 or 8)                | 3.3 (± 1.21)            | 3.3 (± 1.06)         |  |  |
| Week 3 (Visit 6 or 9)                | 3.4 (± 1.18)            | 3.4 (± 1.02)         |  |  |

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Equivalence Ratio OXN60/30 Interim          |
| Statistical analysis description:<br>LST:HST ratio for OXN 60/30 dose interim analysis |   |
| Comparison groups  | OXN60/30 LST Interim v OXN60/30 HST Interim |
| Number of subjects included in analysis  | 40  |
| Analysis specification   | Pre-specified                               |
| Analysis type  | equivalence <sup>[6]</sup>                  |
| Parameter estimate   | Ratio (LST:HST)                             |
| Point estimate   | 1.02  |
| Confidence interval  |   |
| level  | Other: 98.75 %                              |
| sides  | 2-sided                                     |
| lower limit  | 0.88  |
| upper limit  | 1.17  |

Notes:

[6] - The average pain over the past 24 hours over the last 2 weeks of each period were analysed following the approach described in Hauschke et al., 1999 for proving equivalence based on the ratio of 2 mean values from a cross-over design. The analysis concluded on equivalence of tested treatments if the two-sided (1- $\alpha$ )% Fieller confidence interval for the ratio of the mean treatment effects (HST/LST) over the last 2 weeks of each period was fully contained in an equivalence range of 80% to 125%.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Equivalence Ratio OXN80/40 Interim          |
| Statistical analysis description:<br>LST:HST ratio for OXN 80/40 dose interim analysis (20 subjects) |   |
| Comparison groups  | OXN80/40 LST Interim v OXN80/40 HST Interim |
| Number of subjects included in analysis  | 40  |
| Analysis specification   | Pre-specified                               |
| Analysis type  | equivalence <sup>[7]</sup>                  |
| Parameter estimate   | Ratio (LST:HST)                             |
| Point estimate   | 0.97  |
| Confidence interval  |   |
| level  | Other: 98.75 %                              |
| sides  | 2-sided                                     |
| lower limit  | 0.86  |
| upper limit  | 1.09  |

Notes:

[7] - The average pain over the past 24 hours over the last 2 weeks of each period were analysed following the approach described in Hauschke et al., 1999 for proving equivalence based on the ratio of 2 mean values from a cross-over design. The analysis concluded on equivalence of tested treatments if the two-sided (1- $\alpha$ )% Fieller confidence interval for the ratio of the mean treatment effects (HST/LST) over the last 2 weeks of each period was fully contained in an equivalence range of 80% to 125%.

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>   | Equivalence Ratio OXN60/30 PPP      |
| Statistical analysis description:<br>LST:HST ratio for OXN 60/30 dose Per Protocol Population (48 subjects) |                                     |
| Comparison groups   | OXN60/30 LST PPP v OXN60/30 HST PPP |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 96                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | equivalence <sup>[8]</sup> |
| Parameter estimate                      | Ratio (LST:HST)            |
| Point estimate                          | 0.96                       |
| Confidence interval                     |                            |
| level                                   | Other: 98.75 %             |
| sides                                   | 2-sided                    |
| lower limit                             | 0.9                        |
| upper limit                             | 1.03                       |

Notes:

[8] - The average pain over the past 24 hours over the last 2 weeks of each period were analysed following the approach described in Hauschke et al., 1999 for proving equivalence based on the ratio of 2 mean values from a cross-over design. The analysis concluded on equivalence of tested treatments if the two-sided (1- $\alpha$ )% Fieller confidence interval for the ratio of the mean treatment effects (HST/LST) over the last 2 weeks of each period was fully contained in an equivalence range of 80% to 125%.

|  |                                     |
|--|-------------------------------------|
| <b>Statistical analysis title</b>                                      | Equivalence Ratio OXN80/40 PPP      |
| Statistical analysis description:                                      |                                     |
| LST:HST ratio for OXN 80/40 dose Per Protocol Population (49 subjects) |                                     |
| Comparison groups  | OXN80/40 HST PPP v OXN80/40 LST PPP |
| Number of subjects included in analysis                                | 98                                  |
| Analysis specification   | Pre-specified                       |
| Analysis type  | equivalence <sup>[9]</sup>          |
| Parameter estimate   | Ratio (LST:HST)                     |
| Point estimate   | 1.05                                |
| Confidence interval  |                                     |
| level  | Other: 98.75 %                      |
| sides  | 2-sided                             |
| lower limit  | 0.97                                |
| upper limit  | 1.13                                |

Notes:

[9] - The average pain over the past 24 hours over the last 2 weeks of each period were analysed following the approach described in Hauschke et al., 1999 for proving equivalence based on the ratio of 2 mean values from a cross-over design. The analysis concluded on equivalence of tested treatments if the two-sided (1- $\alpha$ )% Fieller confidence interval for the ratio of the mean treatment effects (HST/LST) over the last 2 weeks of each period was fully contained in an equivalence range of 80% to 125%.

### **Primary: Equivalence of bowel function between LST an HST treatment**

|   |  |
|---|--|
| End point title   | Equivalence of bowel function between LST an HST treatment |
| End point description:  |  |
| BFI, as assessed at Visits 5 and 6 and at Visits 8 and 9, respectively. The BFI was the mean of the following items: Ease of defecation (NAS, 0=easy/no difficulty; 100=severe difficulty), Feeling of incomplete bowel evacuation (NAS, 0=not at all, 100=very strong), Personal judgement of constipation (NAS, 0=not at all, 100=very strong). |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| 3 weeks, assessed after 2 and 3 weeks.  |  |

| End point values                     | OXN80/40 LST PPP     | OXN80/40 HST PPP     | OXN60/30 HST PPP     | OXN60/30 LST PPP     |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 68                   | 68                   | 68                   | 68                   |
| Units: Bowel Function Index (BFI)    |                      |                      |                      |                      |
| arithmetic mean (standard deviation) |                      |                      |                      |                      |
| Week 2 (Visit 5 or 8)                | 23.191 (± 23.2139)   | 23.039 (± 24.0914)   | 25.662 (± 23.6688)   | 23.971 (± 22.503)    |
| Week 3 (Visit 6 or 9)                | 25.206 (± 26.0478)   | 23.73 (± 22.5886)    | 23.172 (± 19.6078)   | 20.466 (± 21.1836)   |

| End point values                     | Total PPP            | All LST PPP          | All HST PPP          |  |
|--------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set |  |
| Number of subjects analysed          | 136                  | 136                  | 136                  |  |
| Units: Bowel Function Index (BFI)    |                      |                      |                      |  |
| arithmetic mean (standard deviation) |                      |                      |                      |  |
| Week 2 (Visit 5 or 8)                | 23.966 (± 22.4976)   | 23.581 (± 22.7798)   | 24.35 (± 23.8288)    |  |
| Week 3 (Visit 6 or 9)                | 23.143 (± 21.4904)   | 22.836 (± 23.7718)   | 23.451 (± 21.0741)   |  |

## Statistical analyses

| Statistical analysis title  | BFI LST:HST ratio 60/30mg treatment |
|---|-------------------------------------|
| Statistical analysis description:   |                                     |
| LST:HST ratio of BFI for subjects in the OXN 60/30mg dose group (68 subjects) |                                     |
| Comparison groups   | OXN60/30 LST PPP v OXN60/30 HST PPP |
| Number of subjects included in analysis                                       | 136                                 |
| Analysis specification  | Pre-specified                       |
| Analysis type   | equivalence <sup>[10]</sup>         |
| Parameter estimate  | Ratio (LST:HST)                     |
| Point estimate  | 1.1                                 |
| Confidence interval   |                                     |
| level   | 95 %                                |
| sides   | 2-sided                             |
| lower limit   | 0.99                                |
| upper limit   | 1.24                                |

Notes:

[10] - The co-primary efficacy analysis on the BFI applied the procedure described in Hauschke et al., 1999 for proving equivalence based on the ratio of two mean values from a cross-over design concluding on equivalence of tested treatments if the two-sided (1-α)% Fieller confidence interval for the expected ratio of the mean treatment effects over the last 2 weeks of each period was fully contained in an equivalence range of 80% to 125%.

| Statistical analysis title  | BFI LST:HST ratio 80/40mg treatment |
|---|-------------------------------------|
| Statistical analysis description:   |                                     |
| LST:HST ratio of BFI for subjects in the OXN 80/40mg dose group (68 subjects) |                                     |
| Comparison groups   | OXN80/40 LST PPP v OXN80/40 HST PPP |



|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 136                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | equivalence <sup>[11]</sup> |
| Parameter estimate                      | Ratio (LST:HST)             |
| Point estimate                          | 0.96                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.87                        |
| upper limit                             | 1.06                        |

Notes:

[11] - The co-primary efficacy analysis on the BFI applied the procedure described in Hauschke et al., 1999 for proving equivalence based on the ratio of two mean values from a cross-over design concluding on equivalence of tested treatments if the two-sided (1- $\alpha$ )% Fieller confidence interval for the expected ratio of the mean treatment effects over the last 2 weeks of each period was fully contained in an equivalence range of 80% to 125%.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | BFI LST:HST ratio all subjects in the PPP |
| Statistical analysis description:   |   |
| LST:HST ratio of BFI for all subjects in the Per Protocol Population (136 subjects) |   |
| Comparison groups   | All LST PPP v All HST PPP                 |
| Number of subjects included in analysis   | 272                                       |
| Analysis specification  | Pre-specified                             |
| Analysis type   | equivalence <sup>[12]</sup>               |
| Parameter estimate  | Ratio (LST:HST)                           |
| Point estimate  | 1.03                                      |
| Confidence interval   |   |
| level   | 95 %                                      |
| sides   | 2-sided                                   |
| lower limit   | 0.96                                      |
| upper limit   | 1.11                                      |

Notes:

[12] - The co-primary efficacy analysis on the BFI applied the procedure described in Hauschke et al., 1999 for proving equivalence based on the ratio of two mean values from a cross-over design concluding on equivalence of tested treatments if the two-sided (1- $\alpha$ )% Fieller confidence interval for the expected ratio of the mean treatment effects over the last 2 weeks of each period was fully contained in an equivalence range of 80% to 125%.

### Other pre-specified: Average Pain over the last 24 hours in the Extension Phase

|  |  |
|--|--|
| End point title  | Average Pain over the last 24 hours in the Extension Phase |
| End point description:   |  |
| The 24 hours pain Numeric Rating Scale (NRS) is commonly used to evaluate pain in subjects with chronic non-malignant and malignant pain and its use is consistent with other studies in this development program. On the Pain Intensity Scale, the average pain over the last 24 hours before the visits was analysed. Pain values were assessed on a scale of 0 (meaning no pain) to 10 (meaning worst imaginable pain). |  |
| End point type   | Other pre-specified  |
| End point timeframe:   |  |
| 24 weeks   |  |

| End point values                     | OXN160/80 mg<br>PR HST | OXN140/70 mg<br>PR HST | OXN120/60 mg<br>PR HST | Total Exposure<br>Safety<br>Population<br>(Extension<br>Phase) |
|--------------------------------------|------------------------|------------------------|------------------------|--|
| Subject group type                   | Reporting group        | Reporting group        | Reporting group        | Subject analysis set   |
| Number of subjects analysed          | 70                     | 2                      | 66                     | 138  |
| Units: units on NRS                  |                        |                        |                        |  |
| arithmetic mean (standard deviation) |                        |                        |                        |  |
| Baseline of the core phase           | 3.6 (± 0.88)           | 3.5 (± 0.71)           | 3.2 (± 1.1)            | 3.4 (± 1)  |
| Baseline Extension Phase             | 3.5 (± 1.26)           | 3 (± 0)                | 3.3 (± 1.04)           | 3.4 (± 1.16)   |
| End of Extension Phase               | 3.8 (± 1.43)           | 2.5 (± 0.71)           | 3.3 (± 1.2)            | 3.5 (± 1.34)   |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Bowel Function Index in the Extension Phase

|   |   |
|---|---|
| End point title   | Bowel Function Index in the Extension Phase |
| End point description:  |   |
| The BFI is a 3-term questionnaire to measure constipation from the patient's perspective. Study personnel asked the subject to rate ease of defecation, feeling of incomplete bowel evacuation and personal judgment of constipation in the last 7 days on a scale of 0 to 100, with lower numbers representing good and higher numbers representing poor bowel function. |   |
| End point type  | Other pre-specified                         |
| End point timeframe:  |   |
| 24 weeks  |   |

| End point values                     | OXN160/80 mg<br>PR HST | OXN140/70 mg<br>PR HST | OXN120/60 mg<br>PR HST | Total Exposure<br>Safety<br>Population<br>(Extension<br>Phase) |
|--------------------------------------|------------------------|------------------------|------------------------|--|
| Subject group type                   | Reporting group        | Reporting group        | Reporting group        | Subject analysis set   |
| Number of subjects analysed          | 70                     | 2                      | 66                     | 138  |
| Units: BFI units                     |                        |                        |                        |  |
| arithmetic mean (standard deviation) |                        |                        |                        |  |
| Baseline Core Study                  | 25.7 (± 23.65)         | 0.5 (± 0.71)           | 25.6 (± 24.81)         | 25.3 (± 24.14)   |
| Baseline Extension Phase             | 24.5 (± 25.96)         | 0.5 (± 0.71)           | 21.6 (± 18.97)         | 22.8 (± 22.79)   |
| End of Extension Phase               | 21.8 (± 23.66)         | 0 (± 0)                | 19.4 (± 16.86)         | 20.3 (± 20.63)   |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Quality of Life Based on EuroQol EQ-5D Extension Phase

|                 |  |
|-----------------|--|
| End point title | Quality of Life Based on EuroQol EQ-5D Extension Phase |
|-----------------|--|

End point description:

The EQ-5D is the most widely used generic preference-based measure of health-related quality of life which produces utility scores anchored at 0 for worst imaginable health state and 1 for best imaginable health state.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

6 weeks Core study plus 24 weeks extension Phase

| End point values                     | OXN160/80 mg<br>PR HST | OXN140/70 mg<br>PR HST | OXN120/60 mg<br>PR HST | Total Exposure<br>Safety<br>Population<br>(Extension<br>Phase) |
|--------------------------------------|------------------------|------------------------|------------------------|--|
| Subject group type                   | Reporting group        | Reporting group        | Reporting group        | Subject analysis set   |
| Number of subjects analysed          | 70                     | 2                      | 66                     | 138  |
| Units: EQ-5D Index score             |                        |                        |                        |  |
| arithmetic mean (standard deviation) |                        |                        |                        |  |
| Baseline Core study                  | 0.4 (± 0.32)           | 0.5 (± 0.47)           | 0.6 (± 0.24)           | 0.5 (± 0.3)  |
| Baseline Extension Phase             | 0.6 (± 0.22)           | 0.6 (± 0.26)           | 0.7 (± 0.13)           | 0.7 (± 0.19)   |
| End of Extension Phase               | 0.5 (± 0.26)           | 1 (± 0)                | 0.7 (± 0.11)           | 0.6 (± 0.21)   |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Events were recorded from the point at which the Informed Consent was signed until 7 days after the subject left the study.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 17.1   |

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | OXN80/40 PR LST |
|-----------------------|-----------------|

Reporting group description:

Subjects who received OXN Low Strength Tablet on a dose level of 80 mg oxycodone and 40 mg naloxone.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | OXN80/40 PR HST |
|-----------------------|-----------------|

Reporting group description:

Subjects who received OXN High Strength Tablet on a dose level of 80 mg oxycodone and 40 mg naloxone.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | OXN60/30 PR LST |
|-----------------------|-----------------|

Reporting group description:

Subjects who received OXN Low Strength Tablet on a dose level of 60 mg oxycodone and 30 mg naloxone.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | OXN60/30 PR HST |
|-----------------------|-----------------|

Reporting group description:

Subjects who received OXN High Strength Tablet on a dose level of 60 mg oxycodone and 30 mg naloxone.

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | OXN160/80 PR HST Extension |
|-----------------------|----------------------------|

Reporting group description:

Subjects in the Extension Phase who received OXN160/80 mg PR HST (OXN 80/40 mg tablets twice daily).

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | OXN120/60 PR HST Extension |
|-----------------------|----------------------------|

Reporting group description:

Subjects in the Extension Phase who received OXN120/60 mg PR HST (OXN 60/30 mg tablets twice daily).

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | OXN140/70 PR HST Extension |
|-----------------------|----------------------------|

Reporting group description:

Subjects in the Extension Phase who received OXN140/70 mg PR HST (one OXN 80/40 mg tablet and one OXN 60/30 mg tablet per day).

| Serious adverse events  | OXN80/40 PR LST                            | OXN80/40 PR HST | OXN60/30 PR LST |
|---|--|-----------------|-----------------|
| Total subjects affected by serious adverse events                   |  |                 |                 |
| subjects affected / exposed   | 2 / 79 (2.53%)                             | 1 / 76 (1.32%)  | 1 / 75 (1.33%)  |
| number of deaths (all causes)                                       | 2  | 0               | 0               |
| number of deaths resulting from adverse events                      | 0  | 0               | 0               |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |                 |                 |
| Lung neoplasm   | Additional description: Not related to IMP |                 |                 |

|   |  |                |                |
|---|--|----------------|----------------|
| subjects affected / exposed                     | 0 / 79 (0.00%)   | 0 / 76 (0.00%) | 1 / 75 (1.33%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          | 0 / 0          |
| Malignant neoplasm progression                  | Additional description: All occurrences unrelated to IMP. Fatal case under OXN80/40 PR HST treatment occurred in the extension phase |                |                |
| subjects affected / exposed                     | 2 / 79 (2.53%)   | 0 / 76 (0.00%) | 0 / 75 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2  | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 2  | 0 / 0          | 0 / 0          |
| Renal neoplasm                                  | Additional description: SAE occurred in the extension phase. Not related to IMP.   |                |                |
| subjects affected / exposed                     | 0 / 79 (0.00%)   | 0 / 76 (0.00%) | 0 / 75 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |  |                |                |
| Acute myocardial infarction                     | Additional description: SAE occurred in the extension phase. Not related to IMP.   |                |                |
| subjects affected / exposed                     | 0 / 79 (0.00%)   | 0 / 76 (0.00%) | 0 / 75 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          | 0 / 0          |
| Coronary Artery disease                         | Additional description: SAE occurred in the extension phase. Not related to IMP.   |                |                |
| subjects affected / exposed                     | 0 / 79 (0.00%)   | 0 / 76 (0.00%) | 0 / 75 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          | 0 / 0          |
| Ischaemic cardiomyopathy                        | Additional description: SAE occurred in the extension phase. Not related to IMP.   |                |                |
| subjects affected / exposed                     | 0 / 79 (0.00%)   | 0 / 76 (0.00%) | 0 / 75 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |  |                |                |
| Petit mal epilepsy                              | Additional description: Not related to IMP   |                |                |
| subjects affected / exposed                     | 1 / 79 (1.27%)   | 0 / 76 (0.00%) | 0 / 75 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |  |                |                |
| Anaemia   | Additional description: Not related to IMP   |                |                |
| subjects affected / exposed                     | 0 / 79 (0.00%)   | 1 / 76 (1.32%) | 0 / 75 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          | 0 / 0          |

|   |  |                |                |
|---|--|----------------|----------------|
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all              |  |                |                |
|   | Additional description: SAE occurred in the extension phase.                     |                |                |
|   | 0 / 79 (0.00%)   | 0 / 76 (0.00%) | 0 / 75 (0.00%) |
|   | 0 / 0  | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders<br>Asthma<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all |  |                |                |
|   | Additional description: SAE occurred in the extension phase. Not related to IMP. |                |                |
|   | 0 / 79 (0.00%)   | 0 / 76 (0.00%) | 0 / 75 (0.00%) |
|   | 0 / 0  | 0 / 0          | 0 / 0          |
| Chronic obstructive pulmonary disease<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                     | Additional description: SAE occurred in the extension phase. Not related to IMP. |                |                |
|   | 0 / 79 (0.00%)   | 0 / 76 (0.00%) | 0 / 75 (0.00%) |
|   | 0 / 0  | 0 / 0          | 0 / 0          |
|   | 0 / 0  | 0 / 0          | 0 / 0          |

| Serious adverse events   | OXN60/30 PR HST  | OXN160/80 PR HST Extension | OXN120/60 PR HST Extension |
|--|--|----------------------------|----------------------------|
| Total subjects affected by serious adverse events  |  |                            |                            |
| subjects affected / exposed  | 0 / 73 (0.00%)   | 3 / 70 (4.29%)             | 5 / 66 (7.58%)             |
| number of deaths (all causes)  | 0  | 1                          | 0                          |
| number of deaths resulting from adverse events   | 0  | 0                          | 0                          |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)<br>Lung neoplasm<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all |  |                            |                            |
|  | Additional description: Not related to IMP   |                            |                            |
|  | 0 / 73 (0.00%)   | 0 / 70 (0.00%)             | 0 / 66 (0.00%)             |
|  | 0 / 0  | 0 / 0                      | 0 / 0                      |
| Malignant neoplasm progression<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | Additional description: All occurrences unrelated to IMP. Fatal case under OXN80/40 PR HST treatment occurred in the extension phase |                            |                            |
|  | 0 / 73 (0.00%)   | 1 / 70 (1.43%)             | 0 / 66 (0.00%)             |
|  | 0 / 0  | 0 / 1                      | 0 / 0                      |
|  | 0 / 0  | 0 / 1                      | 0 / 0                      |
| Renal neoplasm<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | Additional description: SAE occurred in the extension phase. Not related to IMP.   |                            |                            |
|  | 0 / 73 (0.00%)   | 0 / 70 (0.00%)             | 1 / 66 (1.52%)             |
|  | 0 / 0  | 0 / 0                      | 0 / 1                      |
|  | 0 / 0  | 0 / 0                      | 0 / 0                      |
| Cardiac disorders  |  |                            |                            |

|   |  |  |  |                |
|---|--|--|--|----------------|
| Acute myocardial infarction                     | Additional description: SAE occurred in the extension phase. Not related to IMP. |  |  |                |
|   | subjects affected / exposed  | 0 / 73 (0.00%)   | 0 / 70 (0.00%)   | 1 / 66 (1.52%) |
|   | occurrences causally related to treatment / all                                  | 0 / 0  | 0 / 0  | 0 / 1          |
|   | deaths causally related to treatment / all                                       | 0 / 0  | 0 / 0  | 0 / 0          |
| Coronary Artery disease                         | Additional description: SAE occurred in the extension phase. Not related to IMP. |  |  |                |
|   | subjects affected / exposed  | 0 / 73 (0.00%)   | 1 / 70 (1.43%)   | 0 / 66 (0.00%) |
|   | occurrences causally related to treatment / all                                  | 0 / 0  | 0 / 1  | 0 / 0          |
|   | deaths causally related to treatment / all                                       | 0 / 0  | 0 / 0  | 0 / 0          |
| Ischaemic cardiomyopathy                        | Additional description: SAE occurred in the extension phase. Not related to IMP. |  |  |                |
|   | subjects affected / exposed  | 0 / 73 (0.00%)   | 0 / 70 (0.00%)   | 1 / 66 (1.52%) |
|   | occurrences causally related to treatment / all                                  | 0 / 0  | 0 / 0  | 0 / 1          |
|   | deaths causally related to treatment / all                                       | 0 / 0  | 0 / 0  | 0 / 0          |
| Nervous system disorders                        |  |  |  |                |
|   | Petit mal epilepsy   | Additional description: Not related to IMP                                       |  |                |
|   | subjects affected / exposed  | 0 / 73 (0.00%)   | 0 / 70 (0.00%)   | 0 / 66 (0.00%) |
|   | occurrences causally related to treatment / all                                  | 0 / 0  | 0 / 0  | 0 / 0          |
|   |  |  |  |                |
|   | deaths causally related to treatment / all                                       | 0 / 0  | 0 / 0  | 0 / 0          |
|   | Blood and lymphatic system disorders   |  |  |                |
|   |  | Anaemia  | Additional description: Not related to IMP                                       |                |
| subjects affected / exposed                     |  | 0 / 73 (0.00%)   | 0 / 70 (0.00%)   | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all |  | 0 / 0  | 0 / 0  | 0 / 0          |
|   |  |  |  |                |
|   | deaths causally related to treatment / all                                       | 0 / 0  | 0 / 0  | 0 / 0          |
|   | Gastrointestinal disorders   |  |  |                |
|   |  | Abdominal pain   | Additional description: SAE occurred in the extension phase.                     |                |
| subjects affected / exposed                     |  | 0 / 73 (0.00%)   | 1 / 70 (1.43%)   | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all |  | 0 / 0  | 1 / 1  | 0 / 0          |
|   |  |  |  |                |
|   | deaths causally related to treatment / all                                       | 0 / 0  | 0 / 0  | 0 / 0          |
|   | Respiratory, thoracic and mediastinal disorders                                  |  |  |                |
|   |  | Asthma   | Additional description: SAE occurred in the extension phase. Not related to IMP. |                |
| subjects affected / exposed                     |  | 0 / 73 (0.00%)   | 0 / 70 (0.00%)   | 1 / 66 (1.52%) |
| occurrences causally related to treatment / all |  | 0 / 0  | 0 / 0  | 0 / 1          |
|   |  |  |  |                |
|   | deaths causally related to treatment / all                                       | 0 / 0  | 0 / 0  | 0 / 0          |
|   | Chronic obstructive pulmonary disease  | Additional description: SAE occurred in the extension phase. Not related to IMP. |  |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 70 (0.00%) | 1 / 66 (1.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |  |  |  |
|---|--|--|--|
| <b>Serious adverse events</b>                                       | OXN140/70 PR HST Extension   |  |  |
| Total subjects affected by serious adverse events                   |  |  |  |
| subjects affected / exposed   | 0 / 2 (0.00%)  |  |  |
| number of deaths (all causes)                                       | 0  |  |  |
| number of deaths resulting from adverse events                      | 0  |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |  |  |
| Lung neoplasm   | Additional description: Not related to IMP   |  |  |
| subjects affected / exposed   | 0 / 2 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0  |  |  |
| deaths causally related to treatment / all                          | 0 / 0  |  |  |
| Malignant neoplasm progression                                      | Additional description: All occurrences unrelated to IMP. Fatal case under OXN80/40 PR HST treatment occurred in the extension phase |  |  |
| subjects affected / exposed   | 0 / 2 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0  |  |  |
| deaths causally related to treatment / all                          | 0 / 0  |  |  |
| Renal neoplasm  | Additional description: SAE occurred in the extension phase. Not related to IMP.   |  |  |
| subjects affected / exposed   | 0 / 2 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0  |  |  |
| deaths causally related to treatment / all                          | 0 / 0  |  |  |
| Cardiac disorders   |  |  |  |
| Acute myocardial infarction   | Additional description: SAE occurred in the extension phase. Not related to IMP.   |  |  |
| subjects affected / exposed   | 0 / 2 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0  |  |  |
| deaths causally related to treatment / all                          | 0 / 0  |  |  |
| Coronary Artery disease   | Additional description: SAE occurred in the extension phase. Not related to IMP.   |  |  |
| subjects affected / exposed   | 0 / 2 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0  |  |  |
| deaths causally related to treatment / all                          | 0 / 0  |  |  |
| Ischaemic cardiomyopathy  | Additional description: SAE occurred in the extension phase. Not related to IMP.   |  |  |



|   |  |  |  |
|---|--|--|--|
| subjects affected / exposed                     | 0 / 2 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |
| Nervous system disorders                        |  |  |  |
| Petit mal epilepsy                              | Additional description: Not related to IMP                                       |  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |
| Blood and lymphatic system disorders            |  |  |  |
| Anaemia   | Additional description: Not related to IMP                                       |  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |
| Gastrointestinal disorders                      |  |  |  |
| Abdominal pain                                  | Additional description: SAE occurred in the extension phase.                     |  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |
| Respiratory, thoracic and mediastinal disorders |  |  |  |
| Asthma  | Additional description: SAE occurred in the extension phase. Not related to IMP. |  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |
| Chronic obstructive pulmonary disease           | Additional description: SAE occurred in the extension phase. Not related to IMP. |  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events                            | OXN80/40 PR LST | OXN80/40 PR HST | OXN60/30 PR LST |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by non-serious adverse events |                 |                 |                 |
| subjects affected / exposed                           | 0 / 79 (0.00%)  | 3 / 76 (3.95%)  | 5 / 75 (6.67%)  |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 79 (0.00%)<br>0 | 1 / 76 (1.32%)<br>1 | 3 / 75 (4.00%)<br>3 |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 79 (0.00%)<br>0 | 1 / 76 (1.32%)<br>1 | 2 / 75 (2.67%)<br>2 |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 79 (0.00%)<br>0 | 1 / 76 (1.32%)<br>1 | 0 / 75 (0.00%)<br>0 |

| <b>Non-serious adverse events</b>  | OXN60/30 PR HST     | OXN160/80 PR HST<br>Extension | OXN120/60 PR HST<br>Extension |
|--|---------------------|-------------------------------|-------------------------------|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                             | 3 / 73 (4.11%)      | 6 / 70 (8.57%)                | 11 / 66 (16.67%)              |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 73 (1.37%)<br>1 | 1 / 70 (1.43%)<br>1           | 3 / 66 (4.55%)<br>3           |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)                         | 2 / 73 (2.74%)<br>2 | 2 / 70 (2.86%)<br>3           | 4 / 66 (6.06%)<br>4           |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 73 (0.00%)<br>0 | 2 / 70 (2.86%)<br>2           | 4 / 66 (6.06%)<br>4           |

| <b>Non-serious adverse events</b>  | OXN140/70 PR HST<br>Extension |  |  |
|--|-------------------------------|--|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed       | 1 / 2 (50.00%)                |  |  |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all) | 1 / 2 (50.00%)<br>1           |  |  |
| Gastrointestinal disorders   |                               |  |  |

|  |                    |  |  |
|--|--------------------|--|--|
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 0 / 2 (0.00%)<br>0 |  |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 2 (0.00%)<br>0 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 06 October 2014  | <p>This Substantial Protocol Amendment added the Pain Intensity Scale – ‘Pain right now’ in the diaries of the Double-blind Phase, and as a further secondary objective of this study.</p> <p>The objective was phrased</p> <ul style="list-style-type: none"><li>• To assess analgesic efficacy at intake of oxycodone/naloxone tablets during the last 2 weeks of each Cross-over Period.</li></ul> <p>Table 1 and its footnotes were changed to include the ‘Pain right now’ documentation in the diary.</p>   |
| 11 December 2014 | <p>This Non-Substantial Protocol Amendment recalculated the CV as requested by the Research Ethics Committee (UK) regarding pain based on clinical study OXN3506 and BFI based on clinical study OXN3401, and adjusted the sample size in accordance therewith.</p> <p>In the sample size estimation for the number of subjects to be analysed for ‘Average pain over the last 24 hours’ the CV between subjects changed from 0.29 to 0.27 and the CV within subjects from 0.29 to 0.15 for the arithmetic average of 2 visits. This changed the required number of evaluable subjects per OXN dose level from 24 subjects to 26 subjects, the total number of subjects from 48 to 52 and the number of subjects in the interim analysis from 36 to 40. For BFI, the CV was recalculated, resulting in a change of CV within subjects from 0.72 to 0.38 for the arithmetic average of 2 visits, and in number of evaluable subjects required to provide a power of <math>\geq 88\%</math> from 84 to 92. Overall the number of subjects to be randomised changed from 132 to 144.</p> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported