# Clinical trial results:
# Effects of oxycodon and venlafaxine on human pain processing. A randomized, double-blinded, placebo-controlled, cross-over study

## Summary

| | |
|---|---|
| EudraCT number | 2013-000170-30 |
| Trial protocol | DK |
| Global end of trial date | 12 December 2014 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 20 June 2021 |
| First version publication date | 20 June 2021 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | MULTIPAIN-2-3-2013 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Aalborg University Hospital |
| Sponsor organisation address | Hobrovej 18-22, Aalborg, Denmark, |
| Public contact | Department of Gastroenterology, Mech-Sense, Aalborg University Hospital, +45 97663562, amd@rn.dk |
| Scientific contact | Department of Gastroenterology, Mech-Sense, Aalborg University Hospital, +45 97663562, amd@rn.dk |

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 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 27 May 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 December 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 December 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to establish a model that is capable of evaluating the effects of analgesics on the pain matrix on both peripheral, spinal, supraspinal, and modulatory level.

Protection of trial subjects:

Subjects were informed verbally and in written about the study before participating and were free to terminate and withdraw from the experiment at any time. Subjects with a history of substance abuse or psychiatric illness were not included in the study. Adverse effects were monitored during the stay at the hospital and after each treatment arm.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 15 April 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Denmark: 20 |
| Worldwide total number of subjects | 20 |
| EEA total number of subjects | 20 |

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) | 20 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Inclusion for the study required medical examinations to be normal, blood pressure below 140/90, no use of medication and Caucasian origin.

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Data analyst, Subject |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | Placebo |

Arm description:

Placebo arm

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

All drugs followed the same administration: on day 1 and day 5 once, and on day 2-4 b.i.d. in total 8 doses. The tablets were produced by the pharmacy at Aarhus University Hospital.

| | |
|---|---|
| **Arm title** | Oxycodone |

Arm description:

Oxycodone arm

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Oxycodone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

10 mg extended release. All drugs followed the same administration: on day 1 and day 5 once, and on day 2-4 b.i.d. in total 8 doses. The tablets were produced by the pharmacy at Aarhus University Hospital.

| | |
|---|---|
| **Arm title** | Venlafaxine |

Arm description:

Venlafaxine arm

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Venlafaxine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Venlafaxine dosages were 37.5mg extended release. All drugs followed the same administration: on day 1 and day 5 once, and on day 2-4 b.i.d. in total 8 doses. The tablets were produced by the pharmacy at Aarhus University Hospital.

| **Number of subjects in period 1** | Placebo | Oxycodone | Venlafaxine |
|---|---|---|---|
| Started | 20 | 20 | 20 |
| Completed | 20 | 20 | 20 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Overall trial |
| Reporting group description: | |
| 20 subjects participated in all treatment arms | |

| Reporting group values | Overall trial | Total | |
|---|---|---|---|
| Number of subjects | 20 | 20 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 20 | 20 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 24.6 | | |
| standard deviation | ± 2.5 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 20 | 20 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: Placebo arm | |
| Reporting group title | Oxycodone |
| Reporting group description: Oxycodone arm | |
| Reporting group title | Venlafaxine |
| Reporting group description: Venlafaxine arm | |

### Primary: Quantitative sensory testing

| | |
|---|---|
| End point title | Quantitative sensory testing |

End point description:

The overall sensory responses were investigated using ice water (the cold pressor test) and electrical stimulations (together with reflex determinations). The mean scores on the visual analogue scale (VAS) for the cold pressor test is presented as end point values for each treatment arm. More details are published by Lelic et al. (Neuropharmacology. 2017. DOI:10.1016/j.neuropharm.2017.06.022) and Lelic et al. (Eur J Neurosci. 2016. DOI: 10.1111/ejn.13443).

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

End point timeframe:

At baseline and after 5 days of treatment

| End point values | Placebo | Oxycodone | Venlafaxine | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20 | 20 | 20 | |
| Units: VAS (no unit) | | | | |
| number (not applicable) | 7.3 | 6.8 | 7.0 | |

### Statistical analyses

| Statistical analysis title | Reflex pain (VAS) |
|---|---|

Statistical analysis description:

Reflex: mixed model with treatment and reflex intensity, mixed model with reflex sensory threshold, reflex threshold and treatment

| | |
|---|---|
| Comparison groups | Placebo v Oxycodone |

| | |
|---|---|
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.552 |
| Method | Mixed models analysis |

| **Statistical analysis title** | Reflex pain (VAS) |
|---|---|

Statistical analysis description:

Reflex: mixed model with treatment and reflex intensity, mixed model with reflex sensory threshold, reflex threshold and treatment

| | |
|---|---|
| Comparison groups | Placebo v Venlafaxine |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.288 |
| Method | Mixed models analysis |

| **Statistical analysis title** | Ice pain (VAS) |
|---|---|

Statistical analysis description:

Ice pain: mixed model with treatment and time

| | |
|---|---|
| Comparison groups | Placebo v Oxycodone |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.036 |
| Method | Mixed models analysis |

## Primary: Electroencephalography

| End point title | Electroencephalography |
|---|---|

End point description:

Electroencephalography (EEG) was recorded during tonic pain stimulation. Spectral analysis and sLORETA source localization were performed in five frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta1 (12-18 Hz) and beta2 (18-32 Hz). The number of frequency bands that were significantly changed after treatment are presented in end point values. Details about the analyses and results are published by Lelic et al. (Neuropharmacology. 2017. doi: 10.1016/j.neuropharm.2017.06.022).

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

End point timeframe:

From baseline and a 5-days treatment

| End point values | Placebo | Oxycodone | Venlafaxine | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20 | 20 | 20 | |
| Units: number of frequency bands, no unit | 0 | 2 | 1 | |

### Statistical analyses

| Statistical analysis title | EEG during tonic pain, placebo |
|---|---|
| Comparison groups | Placebo v Oxycodone v Venlafaxine |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other[1] |
| P-value | > 0.05 |
| Method | t-test, 2-sided |

Notes:

[1] - Data from baseline and after five days of treatment were compared for the placebo arm and no changes were observed.

| Statistical analysis title | EEG during tonic pain, oxycodone |
|---|---|
| Comparison groups | Oxycodone v Venlafaxine v Placebo |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other[2] |
| P-value | < 0.05 [3] |
| Method | t-test, 2-sided |

Notes:

[2] - Data from baseline and after five days of treatment were compared for the oxycodone arm.

[3] - Oxycodone decreased the spectral indices and brain source activity in delta and theta frequency bands.

| Statistical analysis title | EEG during tonic pain, venlafaxine |
|---|---|
| Comparison groups | Venlafaxine v Oxycodone v Placebo |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other[4] |
| P-value | < 0.05 [5] |
| Method | t-test, 2-sided |

Notes:

[4] - Data from baseline and after five days of treatment were compared for the venlafaxine arm.

[5] - Venlafaxine decreased spectral indices in one frequency band (alpha) of the EEG during tonic pain.

### Primary: Nociceptive withdrawel reflex

| End point title | Nociceptive withdrawel reflex |
|---|---|

End point description:

Nociceptive withdrawel reflex (NWR) was elicited under the sole of the foot. Both sensory threshold an reflex threshold was found. The following intensities were used for pain ratings:

- 1.0 x reflex threshold
- 1.3 x reflex threshold
- 1.6 x reflex threshold

5 runs with 18 reflex stimulations in randomized intensity were applied for electromyography (EMG) recordings to assess the spinal (lumbar) response to pain and brain analysis with EEG evoked potentials

was done to the same stimulations.

The mean NWR thresholds after treatments are presented together with the statistical analysis of NWR area under the curve (AUCs).
Details about the analyses and results are published by Lelic et al. (Eur J Neurosci. 2016. doi: 10.1111/ejn.13443.)

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

End point timeframe:

From baseline and a 5-days treatment

| **End point values** | Placebo | Oxycodone | Venlafaxine | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20 | 20 | 20 | |
| Units: mA | | | | |
| number (not applicable) | 14.5 | 12.7 | 14.2 | |

### Statistical analyses

| **Statistical analysis title** | NWR AUC |
|---|---|

Statistical analysis description:

Details are published by Lelic et al. (Eur J Neurosci. 2016. doi: 10.1111/ejn.13443)

| Comparison groups | Placebo v Oxycodone v Venlafaxine |
|---|---|
| Number of subjects included in analysis | 60 |
| Analysis specification | Post-hoc |
| Analysis type | other |
| P-value | < 0.05 [6] |
| Method | ANOVA |

Notes:

[6] - Venlafaxine decreased the NWR AUC, and no differences were observed in the placebo or oxycodone arms

### Primary: Median nerve stimulation

| End point title | Median nerve stimulation |
|---|---|

End point description:

Median nerve stimulation was elicited on the right wrist, and both spinal (cervical) evoked potential (just above C7) to assess the upstream activity, and brain (EEG) evoked potentials were recorded. The sensory and twitch of the thumb thresholds were taken. Then two runs of 1000 stimulations (two per second) were done for spinal and evoked EEG recordings.
Sensory thresholds to median nerve stimulation after treatments are provided and more details about analyses and results are published by Lelic et al. (Br J Clin Pharmacol. 2017. doi: 10.1111/bcp.13177).

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

End point timeframe:

From baseline and a 5-days treatment

| End point values | Placebo | Oxycodone | Venlafaxine | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20 | 20 | 20 | |
| Units: mA | | | | |
| number (confidence interval 95%) | 2.7 (2.4 to 3.0) | 2.5 (2.2 to 2.8) | 2.6 (2.4 to 2.8) | |

**Statistical analyses**

| Statistical analysis title | Median nerve stimulation sensory data |
|---|---|

Statistical analysis description:

Two-way repeated measures analysis of variance with time point and treatment as the two factors were performed and no differences in sensory thresholds were identified.

| Comparison groups | Placebo v Oxycodone v Venlafaxine |
|---|---|
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | > 0.05 |
| Method | ANOVA |

**Primary: MR spectroscopy**

| End point title | MR spectroscopy |
|---|---|

End point description:

MR spectroscopy was performed during rest at baseline and during treatments in the anterior cingulate cortex, insula and prefrontal cortex. Mean glutamate/creatine ratios from the anterior cingulate cortex are presented as end point values and statistics are provided including all three brain areas. More details about the analyses and results are published by Hansen et al. (J Neuroimaging. 2016. doi: 10.1111/jon.12345.)

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

End point timeframe:

From baseline and after a 5-day treatment

| End point values | Placebo | Oxycodone | Venlafaxine | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 19 | 19 | 20 | |
| Units: no units (ratio) | | | | |
| number (not applicable) | 1.35 | 1.29 | 1.32 | |

**Statistical analyses**

| Statistical analysis title | Glutamate/creatine changes oxycodone vs placebo |
|---|---|

Statistical analysis description:

The change in glutamate/creatine following oxycodone was calculated as compared to the measurement

before treatment and compared to placebo.

| | |
|---|---|
| Comparison groups | Oxycodone v Placebo |
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | other[7] |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | percentage |
| Point estimate | -8.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.2 |
| upper limit | -1.7 |
| Variability estimate | Standard deviation |
| Dispersion value | 0.3 |

Notes:

[7] - A mixed effect model with treatment type and area as fixed effects (full factorial) and subject as a random effect was used.

| **Statistical analysis title** | Glutamate/creatine changes venlafaxine vs placebo |
|---|---|

Statistical analysis description:

The level of glutamate/creatine following venlafaxine was calculated as compared to the measurement before treatment and compared to placebo.

| | |
|---|---|
| Comparison groups | Venlafaxine v Placebo |
| Number of subjects included in analysis | 39 |
| Analysis specification | Post-hoc |
| Analysis type | other[8] |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | percentage |
| Point estimate | -6.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.5 |
| upper limit | 0.2 |
| Variability estimate | Standard deviation |
| Dispersion value | 0.4 |

Notes:

[8] - A mixed effect model with treatment type and area as fixed effects (full factorial) and subject as a random effect was used.

## Secondary: Offset analgesia

| End point title | Offset analgesia |
|---|---|

End point description:

Offset analgesia (OA) was induced with a thermode on the arm. To determine the pain tolerance threshold, the temperature was slowly increased from 35ºC at 1.5ºC per second rate and the volunteers pressed a button when they reached their individual pain tolerance threshold. Offset analgesia magnitude (in percentage) was calculated as delta_VAS normalized with respect to peak value ((delta_VAS/peak)*100)) and presented.

| End point type | Secondary |
|---|---|

End point timeframe:

From baseline and after 5-days treatment

| End point values | Placebo | Oxycodone | Venlafaxine | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20 | 20 | 20 | |
| Units: percent | | | | |
| number (not applicable) | 60.3 | 69.3 | 61.2 | |

## Statistical analyses

| Statistical analysis title | Offset analgesia magnitude |
|---|---|

Statistical analysis description:

Offset analgesia magnitude (in percentage) was calculated as delta_VAS normalized with respect to peakvalue ((delta_VAS/peak)*100)). The average baseline values were calculated as a mean of the three baseline measurements for each participant. A repeated measures regression with treatment as random effect was used.
Detailed analysis description and results are published elsewhere (Olesen et al. Basic Clin Pharmacol Toxicol. 2018. doi: 10.1111/bcpt.13078).

| | |
|---|---|
| Comparison groups | Placebo v Oxycodone v Venlafaxine |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Variability estimate | Standard deviation |

## Secondary: Resting state MRI

| End point title | Resting state MRI |
|---|---|

End point description:

Resting state magnetic resonance imaging was performed and functional connectivity analyses were explored between four predefined seeds (dorsal anterior cingulate cortex, rostral anterior cingulate cortex, posterior insula, and prefrontal cortex), and the whole brain. The number of seeds that revealed changed connectivity is presented. Details about the analyses and results are published by Hansen et al. (CNS Neurosci Ther. 2018. doi: 10.1111/cns.12827.)

| End point type | Secondary |
|---|---|

End point timeframe:

From baseline and after a 5-day treatment

| End point values | Placebo | Oxycodone | Venlafaxine | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20 | 18 | 19 | |
| Units: Number of seeds affected | 4 | 4 | 4 | |

## Statistical analyses

| Statistical analysis title | Functional connectivity oxycodone vs placebo |
|---|---|

Statistical analysis description:

Treatment effects were investigated in four predefined seeds to the whole brain.

| | |
|---|---|
| Comparison groups | Oxycodone v Placebo |
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [9] |
| Method | t-test, 2-sided |

Notes:

[9] - The main results were that oxycodone decreased functional connectivity between limbic structures and to supra limbic areas.

| Statistical analysis title | Functional connectivity venlafaxine vs placebo |
|---|---|

Statistical analysis description:

Treatment effects were investigated in four predefined seeds to the whole brain.

| | |
|---|---|
| Comparison groups | Placebo v Venlafaxine |
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [10] |
| Method | t-test, 2-sided |

Notes:

[10] - The main results were that venlafaxine decreased functional connectivity between limbic structures and to supralimbic areas, and increased functional connectivity to structures in the midbrain and brain stem.

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| November 2013 - December 2014 | |
| Adverse event reporting additional description: | |
| All the non-serious adverse events were known side-effects to the treatments.<br>More details about side-effects are published in | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 23 |

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo was administered once on day 1 and day 5, and twice a day on day 2-4, in total eight doses with 12 hours in between. | |
| Reporting group title | Oxycodone |
| Reporting group description: | |
| Oxycodone (10 mg extended release) was administered orally as tablets once on day 1 and day 5 and twice on day 2-4 in total eight doses with 12 hours in between. | |
| Reporting group title | Venlafaxine |
| Reporting group description: | |
| Venlafaxine (37.5 mg extended release) was administered orally once on day 1 and day 5, and twice a day on day 2-4, in total eight doses with 12 hours in between. | |

| Serious adverse events | Placebo | Oxycodone | Venlafaxine |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 20 (0.00%) | 0 / 20 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

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

| Non-serious adverse events | Placebo | Oxycodone | Venlafaxine |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 20 (20.00%) | 17 / 20 (85.00%) | 18 / 20 (90.00%) |
| Cardiac disorders | | | |
| Heart rate increased | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Headache | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 2 / 20 (10.00%) | 4 / 20 (20.00%) |
| occurrences (all) | 2 | 2 | 4 |
| General disorders and administration site conditions | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 4 / 20 (20.00%) | 6 / 20 (30.00%) |
| occurrences (all) | 0 | 4 | 6 |
| Sedation | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 8 / 20 (40.00%) | 5 / 20 (25.00%) |
| occurrences (all) | 2 | 8 | 5 |
| Discomfort | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 5 / 20 (25.00%) | 8 / 20 (40.00%) |
| occurrences (all) | 0 | 5 | 8 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 3 / 20 (15.00%) | 10 / 20 (50.00%) |
| occurrences (all) | 0 | 3 | 10 |
| Mouth dryness | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 20 (0.00%) | 8 / 20 (40.00%) |
| occurrences (all) | 0 | 0 | 8 |
| Constipation | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Low appetite | | | |
| alternative dictionary used: n/a 0 | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) | 2 / 20 (10.00%) |
| occurrences (all) | 1 | 0 | 2 |
| Skin and subcutaneous tissue disorders | | | |
| Itching | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 6 / 20 (30.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Sweating | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 2 / 20 (10.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/28648913

http://www.ncbi.nlm.nih.gov/pubmed/29938898

http://www.ncbi.nlm.nih.gov/pubmed/27748551

http://www.ncbi.nlm.nih.gov/pubmed/27028269

http://www.ncbi.nlm.nih.gov/pubmed/27808426

http://www.ncbi.nlm.nih.gov/pubmed/29468854