



## Clinical trial results:

### Use of long acting opioids for pre- and postoperative analgesia in primary total knee arthroplasty. A double-blinded randomized control trial. Tapentadol vs Oxycodon vs Placebo

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2015-000295-94   |
| Trial protocol           | NO               |
| Global end of trial date | 28 February 2019 |

#### Results information

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| Result version number             | v1 (current)                        |
| This version publication date     | 29 November 2021                    |
| First version publication date    | 29 November 2021                    |
| Summary attachment (see zip file) | Summary 121121 (Summary 121121.pdf) |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | TPO-150 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02604446 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                       |
|------------------------------|-------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | St. Olavs Hospital, Trondheim, Norway                                                                 |
| Sponsor organisation address | Olav Kyrrs gate, Trondheim, Norway, 7006                                                              |
| Public contact               | Head of Clinic, Orthopedic surgery, St. Olavs University Hospital, +47 72823244, knut.hagen@stolav.no |
| Scientific contact           | Head of Clinic, Orthopedic surgery, St. Olavs University Hospital, +47 72823244, knut.hagen@stolav.no |

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                       | 28 February 2019 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 28 February 2019 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 28 February 2019 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

Primary objective of the trial is to measure variations in pain relief between three different pain treatments

Protection of trial subjects:

Before surgery, all patients received acetaminophen tablets 2/ 1.5 g above/below 70 kg, dexamethasone tablets 20/16 mg above/below 70 kg, naproxen 500 mg 1 esomeprazole 20 mg. Acetaminophen, naproxen and esomeprazole were repeated on the day of surgery. After the day of surgery, patients received study medication twice daily, naproxen 500 mg 1 esomeprazole 20 mg twice daily, and acetaminophen 1000 mg 4 times daily for 6 days. For rescue analgesia, patients in all 3 study groups had the opportunity to take oral oxycodone immediate-release (IR) 5 mg on demand.

Background therapy:

Acetaminophen tablets 2/ 1.5 g above/below 70 kg, dexamethasone tablets 20/16 mg above/below 70 kg, naproxen 500 mg 1 esomeprazole 20 mg. Acetaminophen, naproxen 1 esomeprazole were repeated on the day of surgery. After the day of surgery, patients received study medication twice daily, naproxen 500 mg 1 esomeprazole 20 mg twice daily, and acetaminophen 1000 mg 4 times daily for 6 days. For rescue analgesia, patients in all 3 study groups had the opportunity to take oral oxycodone immediate-release (IR) 5 mg on demand.

Evidence for comparator:

Opioids are effective drugs for pain relief, with increased efficacy with increased doses. Tapentadol is an analgesic drug that provides analgesia through both the opioid and alpha-2-adrenergic receptors

|                                                           |                   |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment                          | 01 September 2015 |
| 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 | Norway: 149 |
| Worldwide total number of subjects   | 149         |
| EEA total number of subjects         | 149         |

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                      | 0   |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Enrollment was done by an anesthesiologist at the preoperative outpatient clinic in the period between September 2015 and February 2019.

### Pre-assignment

Screening details:

Patients scheduled for surgery with TKA between 18 and 80 years of age were included in the study.

### Period 1

|                              |                                    |
|------------------------------|------------------------------------|
| Period 1 title               | Drug intervention (overall period) |
| Is this the baseline period? | Yes                                |
| Allocation method            | Randomised - controlled            |
| Blinding used                | Double blind <sup>[1]</sup>        |
| Roles blinded                | Subject, Monitor, Carer, Assessor  |

Blinding implementation details:

Randomization was performed by the Unit for Applied Clinical Research (AKF NTNU). Computer-generated block randomization with block sizes of 30, 30, 30, 21, 21, and 18 was used. The randomization of study drugs was only known by the hospital pharmacy (for emergency unblinding), the monitor unit (AKF NTNU) who generated the list, and the manufacturer of the study drugs. The 3 different study drugs were packed in identical resorbable capsules and swallowed whole. Ward staff did all handling.

### Arms

|                              |               |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes           |
| <b>Arm title</b>             | Placebo group |

Arm description:

Placebo drug x 2 Day of surgery and day 1-6

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

Dosage and administration details:

Tapentadol 50 mg x 2

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

Dosage and administration details:

1 tablet x 2 in seven days

|                  |            |
|------------------|------------|
| <b>Arm title</b> | Tapentadol |
|------------------|------------|

Arm description:

tapentadol 50 mg x 2 for seven days

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

|                                        |            |
|----------------------------------------|------------|
| Investigational medicinal product name | Tapentadol |
| Investigational medicinal product code |            |
| Other name                             | Tapentadol |
| Pharmaceutical forms                   | Tablet     |
| Routes of administration               | Oral use   |

Dosage and administration details:

Tapentadol 50 mg x 2

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | Oxycodone |
|------------------|-----------|

Arm description:

Oxycodone 19 mg x 2 for seven days

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | oxycodone         |
| Investigational medicinal product code |                   |
| Other name                             | oxycodone         |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

oxycodone 20 mg x 2 for seven days

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: The randomization of study drugs was only known by the hospital pharmacy (for emergency unblinding), the monitor unit (AKF NTNU) who generated the list, and the manufacturer of the study

drugs. The 3 different study drugs were packed in identical resorbable capsules and swallowed whole.

Ward staff did all handling of study drugs and other analgesic drugs in the study. All participants, healthcare personnel, and investigators were blinded for the study drug allocation.

| <b>Number of subjects in period 1</b> | Placebo group | Tapentadol | Oxycodone |
|---------------------------------------|---------------|------------|-----------|
| Started                               | 50            | 49         | 50        |
| Completed                             | 50            | 49         | 50        |

## Baseline characteristics

### Reporting groups

|                                                                             |               |
|-----------------------------------------------------------------------------|---------------|
| Reporting group title                                                       | Placebo group |
| Reporting group description:<br>Placebo drug x 2 Day of surgery and day 1-6 |               |
| Reporting group title                                                       | Tapentadol    |
| Reporting group description:<br>tapentadol 50 mg x 2 for seven days         |               |
| Reporting group title                                                       | Oxycodone     |
| Reporting group description:<br>Oxycodone 19 mg x 2 for seven days          |               |

| Reporting group values | Placebo group | Tapentadol | Oxycodone |
|------------------------|---------------|------------|-----------|
| Number of subjects     | 50            | 49         | 50        |
| Age categorical        |               |            |           |
| Age                    |               |            |           |
| Units: Subjects        |               |            |           |
| Adults (18-64 years)   | 50            | 49         | 50        |
| Gender categorical     |               |            |           |
| Units: Subjects        |               |            |           |
| Female                 | 7             | 1          | 1         |
| Male                   | 43            | 48         | 49        |

| Reporting group values | Total |  |  |
|------------------------|-------|--|--|
| Number of subjects     | 149   |  |  |
| Age categorical        |       |  |  |
| Age                    |       |  |  |
| Units: Subjects        |       |  |  |
| Adults (18-64 years)   | 149   |  |  |
| Gender categorical     |       |  |  |
| Units: Subjects        |       |  |  |
| Female                 | 9     |  |  |
| Male                   | 140   |  |  |

## End points

### End points reporting groups

|                                                                             |               |
|-----------------------------------------------------------------------------|---------------|
| Reporting group title                                                       | Placebo group |
| Reporting group description:<br>Placebo drug x 2 Day of surgery and day 1-6 |               |
| Reporting group title                                                       | Tapentadol    |
| Reporting group description:<br>tapentadol 50 mg x 2 for seven days         |               |
| Reporting group title                                                       | Oxycodone     |
| Reporting group description:<br>Oxycodone 19 mg x 2 for seven days          |               |

### Primary: Pain at day seven

|                                                                                                                                                                                                                                                                                                                                          |                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| End point title                                                                                                                                                                                                                                                                                                                          | Pain at day seven |
| End point description:<br>The patients were asked "How much pain do you have now when you move, where 0 is no pain and 10 is the worst pain imaginable." The primary outcome is reported as area under the pain curve (AUC) and the corresponding mean value of pain for each patient and the groups for the first 7 postoperative days. |                   |
| End point type                                                                                                                                                                                                                                                                                                                           | Primary           |
| End point timeframe:<br>Seven days                                                                                                                                                                                                                                                                                                       |                   |

| End point values            | Placebo group     | Tapentadol        | Oxycodone         |  |
|-----------------------------|-------------------|-------------------|-------------------|--|
| Subject group type          | Reporting group   | Reporting group   | Reporting group   |  |
| Number of subjects analysed | 43 <sup>[1]</sup> | 45 <sup>[2]</sup> | 46 <sup>[3]</sup> |  |
| Units: Area under the curve |                   |                   |                   |  |
| Pain                        | 528               | 427               | 508               |  |

Notes:

[1] - 7 without follow-up data

[2] - 4 without follow-up data

[3] - 4 without follow-up data

### Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                        |                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                                                             | Kruskal-Wallis                         |
| Statistical analysis description:<br>For pain on mobilization and pain at rest, AUC was calculated and divided by elapsed time from first to last postoperative measurement from the first to the seventh day to yield a measure of mean pain in this period. Mean pain was then compared between the experimental groups using the nonparametric Kruskal-Wallis test. |                                        |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                      | Placebo group v Tapentadol v Oxycodone |

|                                         |                                  |
|-----------------------------------------|----------------------------------|
| Number of subjects included in analysis | 134                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | < 0.05 <sup>[4]</sup>            |
| Method                                  | Kruskal-wallis                   |
| Parameter estimate                      | Median difference (final values) |
| Point estimate                          | 0.12                             |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | 0.1                              |
| upper limit                             | 0.14                             |
| Variability estimate                    | Standard deviation               |
| Dispersion value                        | 204                              |

Notes:

[4] - No statistical difference found between the group for prarimary (or secobdary) outcome (P=12)



## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

14 days

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |   |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Placebo group |
|-----------------------|---------------|

Reporting group description:

Placebo drug x 2 Day of surgery and day 1-6

|                       |            |
|-----------------------|------------|
| Reporting group title | Tapentadol |
|-----------------------|------------|

Reporting group description:

tapentadol 50 mg x 2 for seven days

|                       |           |
|-----------------------|-----------|
| Reporting group title | Oxycodone |
|-----------------------|-----------|

Reporting group description:

Oxycodone 19 mg x 2 for seven days

| Serious adverse events                            | Placebo group  | Tapentadol     | Oxycodone      |
|---------------------------------------------------|----------------|----------------|----------------|
| Total subjects affected by serious adverse events |                |                |                |
| subjects affected / exposed                       | 0 / 43 (0.00%) | 0 / 45 (0.00%) | 0 / 45 (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 group  | Tapentadol     | Oxycodone      |
|-------------------------------------------------------|----------------|----------------|----------------|
| Total subjects affected by non-serious adverse events |                |                |                |
| subjects affected / exposed                           | 0 / 43 (0.00%) | 0 / 45 (0.00%) | 0 / 45 (0.00%) |

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No adverse event occurred more frequent than 5%. Constipation occurred more frequent in the oxycodone group than the other groups (p=0.02)

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

|                                                                                                           |
|-----------------------------------------------------------------------------------------------------------|
| The sample size of 150 patients was not large enough to rule out a small difference of in pain NRS scores |
|-----------------------------------------------------------------------------------------------------------|

Notes: