



## Clinical trial results:

### Remifentanyl tapering and post-adenotonsillectomy pain in children: a randomised, placebo controlled, double blind study

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2019-001677-81 |
| Trial protocol           | NO             |
| Global end of trial date |                |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 03 November 2023 |
| First version publication date | 03 November 2023 |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | PTRS01 |
|-----------------------|--------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03994146 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Akershus Universitetssykehus  |
| Sponsor organisation address | Sykehusveien 25, Lørenskog, Norway, 1478  |
| Public contact               | Principal Investigator, Akershus Universitetssykehus,<br>william.james.morton@ahus.no |
| Scientific contact           | Principal Investigator, Akershus Universitetssykehus,<br>william.james.morton@ahus.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                                       | Interim         |
| Date of interim/final analysis                       | 18 October 2023 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | No              |

Notes:

## General information about the trial

Main objective of the trial:

Tonsillectomy is the commonest operation of childhood and results in considerable pain. Remifentanyl is a potent, ultra short acting opioid with a long- established safety record in paediatric anaesthesia that is used to provide intraoperative analgesia. There is evidence from adult studies that remifentanyl paradoxically increases postoperative pain, although this may be ablated if propofol (rather than inhalational anaesthesia) is used or if the remifentanyl is tapered rather than abruptly discontinued at the end of surgery. The analgesic effect of gradual withdrawal of remifentanyl at the end of surgery has not been studied in children and may have significant clinical implications. The primary measure of efficacy will be the dose of fentanyl rescue analgesia in the perioperative period (1 mcg.kg<sup>-1</sup> bolus for >20% increase in pulse, blood pressure or movement intraoperatively or a FLACC(Face, Legs, Arms, Cry, Consolability) score of >5 in the recovery unit.

Protection of trial subjects:

Independent clinician.

National data handling agreement.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 06 January 2020 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Norway: 12 |
| Worldwide total number of subjects   | 12         |
| EEA total number of subjects         | 12         |

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)                     | 12 |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 0  |

|                     |   |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over   | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Trial prematurely terminated due to poor recruitment.

### Pre-assignment

Screening details:

American Society Anaesthesiology I-II children (1 to 10 years)

Weight over 10.0 kg

Presenting for tonsillectomy / tonsillotomy or adenotonsillectomy / tonsillotomy at Akershus

Universitetssykehus, Lørenskog, or Lovisenberg Diakonale Hospital, Oslo, Norway

### Period 1

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

Blinding implementation details:

Blinding conducted by sealed envelop.

### Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | Yes  |
| <b>Arm title</b>             | Remifentanil tapering / Placebo abrupt cessation |

Arm description:

Syringe one contains Remifentanil 2 mg in 40 ml NaCl 9 mg.ml<sup>-1</sup> = 50 µg.ml<sup>-1</sup> which will be infused at a rate of 0.9 µg.kg<sup>-1</sup>.min<sup>-1</sup> and Syringe two contains 40 ml NaCl 9 mg.ml<sup>-1</sup> at an identical infusion rate. According to randomisation syringe one will then be tapered towards the end of surgery and syringe two abruptly stopped.

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Remifentanil           |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravascular use      |

Dosage and administration details:

Remifentanil 2 mg in 40 ml NaCl 9 mg.ml<sup>-1</sup> = 50 µg.ml<sup>-1</sup>  
infused at a rate of 0.9 µg.kg<sup>-1</sup>.min<sup>-1</sup>

|                  |   |
|------------------|---|
| <b>Arm title</b> | Placebo Tapering / Remifentanil Abrupt cessation. |
|------------------|---|

Arm description:

Syringe one contains 40 ml NaCl 9 mg.ml<sup>-1</sup> and Syringe two contains Remifentanil 2 mg in 40 ml NaCl 9 mg.ml<sup>-1</sup> = 50 µg.ml<sup>-1</sup> which will be infused at a rate of 0.9 µg.kg<sup>-1</sup>.min<sup>-1</sup>. According to randomization syringe one will be tapered towards the end of surgery and syringe two abruptly stopped

|  |                        |
|--|------------------------|
| Arm type                               | Active comparator      |
| Investigational medicinal product name | Normal Saline 0.9%     |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravascular use      |

Dosage and administration details:

40 ml NaCl 9 mg.ml<sup>-1</sup>

| <b>Number of subjects in period 1</b> | Remifentanil tapering / Placebo abrupt cessation | Placebo Tapering / Remifentanil Abrupt cessation. |
|---------------------------------------|--|---|
| Started                               | 6  | 6   |
| Completed                             | 6  | 6   |

## Baseline characteristics

## End points

### End points reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Remifentanil tapering / Placebo abrupt cessation |
|-----------------------|--|

Reporting group description:

Syringe one contains Remifentanil 2 mg in 40 ml NaCl 9 mg.ml<sup>-1</sup> = 50 µg.ml<sup>-1</sup> which will be infused at a rate of 0.9 µg.kg<sup>-1</sup>.min<sup>-1</sup> and Syringe two contains 40 ml NaCl 9 mg.ml<sup>-1</sup> at an identical infusion rate. According to randomisation syringe one will then be tapered towards the end of surgery and syringe two abruptly stopped.

|                       |   |
|-----------------------|---|
| Reporting group title | Placebo Tapering / Remifentanil Abrupt cessation. |
|-----------------------|---|

Reporting group description:

Syringe one contains 40 ml NaCl 9 mg.ml<sup>-1</sup> and Syringe two contains Remifentanil 2 mg in 40 ml NaCl 9 mg.ml<sup>-1</sup> = 50 µg.ml<sup>-1</sup> which will be infused at a rate of 0.9 µg.kg<sup>-1</sup>.min<sup>-1</sup>. According to randomization syringe one will be tapered towards the end of surgery and syringe two abruptly stopped

### Primary: Premature trial termination due to poor recruitment

|                 |   |
|-----------------|---|
| End point title | Premature trial termination due to poor recruitment |
|-----------------|---|

End point description:

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

End point timeframe:

06.01-2020 to 22.12.2021

| End point values            | Remifentanil tapering / Placebo abrupt cessation | Placebo Tapering / Remifentanil Abrupt cessation. |  |  |
|-----------------------------|--|---|--|--|
| Subject group type          | Reporting group                                  | Reporting group                                   |  |  |
| Number of subjects analysed | 6 <sup>[1]</sup>                                 | 6   |  |  |
| Units: 0                    | 0  | 0   |  |  |

Notes:

[1] - Premature trial termination due to poor recruitment

### Statistical analyses

|                            |                             |
|----------------------------|-----------------------------|
| Statistical analysis title | Premature trial termination |
|----------------------------|-----------------------------|

Statistical analysis description:

No statistical analysis due to premature trial termination due to poor recruitment.

|                   |  |
|-------------------|--|
| Comparison groups | Remifentanil tapering / Placebo abrupt cessation v Placebo Tapering / Remifentanil Abrupt cessation. |
|-------------------|--|

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 12                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[2]</sup> |
| P-value                                 | < 0.05 <sup>[3]</sup>      |
| Method                                  | Kruskal-wallis             |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | 10                         |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 1-sided                    |
| lower limit                             | 5                          |
| Variability estimate                    | Standard deviation         |
| Dispersion value                        | 10                         |

Notes:

[2] - No statistical analysis due to premature trial termination due to poor recruitment.

[3] - No statistical analysis due to premature trial termination due to poor recruitment.



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

06.01.2020 to 22.12.2021

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

### Dictionary used

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

|                    |     |
|--------------------|-----|
| Dictionary version | 2.1 |
|--------------------|-----|

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Remifenatil Tapering |
|-----------------------|----------------------|

Reporting group description: -

| Serious adverse events                            | Remifenatil Tapering |  |  |
|---|----------------------|--|--|
| Total subjects affected by serious adverse events |                      |  |  |
| subjects affected / exposed                       | 0 / 12 (0.00%)       |  |  |
| number of deaths (all causes)                     | 0                    |  |  |
| number of deaths resulting from adverse events    | 0                    |  |  |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events                            | Remifenatil Tapering   |  |  |
|---|--|--|--|
| Total subjects affected by non-serious adverse events |  |  |  |
| subjects affected / exposed                           | 1 / 12 (8.33%)   |  |  |
| Surgical and medical procedures                       |  |  |  |
| Surgical failure                                      | Additional description: Surgical time to achieve haemostasis necessitated an unplanned overnight stay for the patient. Not related to trial. |  |  |
| subjects affected / exposed                           | 1 / 12 (8.33%)   |  |  |
| occurrences (all)                                     | 1  |  |  |

## 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

None reported