



## Clinical trial results:

### Preanesthetic medication in pediatric patients: A comparison of midazolam, clonidine and dexmedetomidine

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-003676-70 |
| Trial protocol           | SE             |
| Global end of trial date | 30 June 2019   |

#### Results information

|                                |  |
|--------------------------------|--|
| Result version number          | v3 (current)   |
| This version publication date  | 01 January 2024  |
| First version publication date | 11 October 2022  |
| Version creation reason        | • Changes to summary attachments<br>Adding links to manuscript 2 and 3 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | PedPreMed |
|-----------------------|-----------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Region Norrbotten   |
| Sponsor organisation address | Robertsviksgatan 7, Luleå, Sweden, 90187                                      |
| Public contact               | Magnus Hultin, Norrbottens läns landsting, 46 920282341, magnus.hultin@umu.se |
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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:

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## Results analysis stage

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 30 June 2019 |
| Is this the analysis of the primary completion data? | No           |
| <hr/>  |              |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 30 June 2019 |
| Was the trial ended prematurely?                     | Yes          |

Notes:

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## General information about the trial

Main objective of the trial:

The aim of this research is to compare three different preanesthetic medications (midazolam, clonidine and dexmedetomidine) in elective minor surgery under total intravenous anesthesia in pediatric patients for anxiolysis and sedation, hemodynamic stability and recovery profiles.

Protection of trial subjects:

The trial was conducted in the normal perioperative pediatric flow at the hospital to ensure a close monitoring of the child while acute effects of the IMPs were studied. One parent was present with the child until the child was anesthetized in the operation theatre. During the preanesthetic phase there was a registered nurse present in the same room until the registered anesthetic nurse (RNA) brought the child and the parent to the operation theatre. During induction of anesthesia and until being delivered to the postoperative ward, and anesthesiologist (registered specialist physician) and the RNA was present all the time. At the postoperative ward a registered nurse attended the needs of the child in addition to having the parent present.

For unexpected long-term effects after the child had left the hospital and the acute effect of the premedication (IMP) was undetectable, the parent had access to a study-telephone number in addition to being able to contact the surgeon or the emergency ward. Information about the trial was added to the patients electronic health registry (chart) and a procedure for breaking the code for the individual patient by opening a sealed envelope was in place 24/7/365 if it would have been necessary. The decision to break the code was left at the discretion of the attending at the intensive care unit of the hospital.

Background therapy:

Preoperative lidocain/prilocain local cream 20 mg/g, 2g, paracetamol 30 mg/kg, ibuprofen oral solution 10 mg/kg, betamethasone, 0.3 mg/kg.

Anesthesia with atropine 0.01 mg/kg iv, propofol and remifentanyl infusion.

Postoperative iv morphine 0.1-0.2 mg/kg and ondansetron 0.1 mg/kg.

Evidence for comparator:

The comparators were three groups receiving oral midazolam, oral clonidine or intranasal dexmedetomidine as preanesthetic medication. Oral dexmedetomidine was not preferred because of poor bioavailability. Results from clinical trials in children, suggests that intranasal administration of dexmedetomidine is more effective as premedication, with adequate sedation achieved within 30 to 45 minutes (Cimen, Hanci, Sivrikaya, Kilinc, & Erol, n.d.; Zhang, Bai, Zhang, Wang, & Lu, 2013). Using oral preanesthetic, onset of sedation is significantly faster after premedication with oral midazolam (30 min) than with oral clonidine (60 min) (Almenrader, Passariello, Coccetti, Haiberger, & Pietropaoli, 2007).

The compared premedications are oral midazolam 0.5 mg/kg, oral clonidine 4 µg/kg, and intranasal dexmedetomidine 2 µg/kg. These products are used "off label" as clinical routine in hospitals in Sweden and worldwide for sedation to children undergoing procedures. Course of therapy are current regimens, tested and recommended in clinical studies and by the Medical Products Agency (Almenrader et al., 2007; Cimen, Hanci, Sivrikaya, Kilinc, & Erol, n.d.; Zhang, Bai, Zhang, Wang, & Lu, 2013).

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 01 February 2017 |
| 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 | Sweden: 90 |
| Worldwide total number of subjects   | 90         |
| EEA total number of subjects         | 90         |

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)                     | 90 |
| 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:

The study took place in Region Norrbotten, Sweden. Patients were recruited between February 1, 2017 and May 6, 2017.

### Pre-assignment

Screening details:

In total, 239 patients aged 2-6 years and planned for ENT surgery were assessed for eligibility. Due to shortness of research staff on the day of surgery (n=199), declined to participate (n=4), not meeting inclusion criteria (n=49) or being removed from the operation program (n=5), only 90 patients were randomized.

### Period 1

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

Blinding implementation details:

A separate nurse, not involved in any of the other roles, performed the randomization by opening a sealed envelope, preparing and giving the three doses: two placebos and one with an active substance.

### Arms

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

Arm description:

Children who received clonidine 4 µg/kg oral solution 60 min before going to surgery

|  |                               |
|--|-------------------------------|
| Arm type                               | Active comparator             |
| Investigational medicinal product name | Clonidine                     |
| Investigational medicinal product code |                               |
| Other name                             |                               |
| Pharmaceutical forms                   | Concentrate for oral solution |
| Routes of administration               | Enteral use                   |

Dosage and administration details:

Clonidine APL, oral solution 20 µg/ml, 4 µg/kg (0.2 ml/kg), given per os 60 min before going to surgery

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | MID group |
|------------------|-----------|

Arm description:

Children who received midazolam 0.5mg/kg oral solution 40 min before going to surgery

|  |                               |
|--|-------------------------------|
| Arm type                               | Active comparator             |
| Investigational medicinal product name | Midazolam                     |
| Investigational medicinal product code |                               |
| Other name                             |                               |
| Pharmaceutical forms                   | Concentrate for oral solution |
| Routes of administration               | Enteral use                   |

Dosage and administration details:

Clonidine APL, oral solution 1 mg/ml, 0.5 mg/kg (0.5 ml/kg), given per os 40 min before going to surgery

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | DEX group |
|------------------|-----------|

Arm description:

Children who received dexmedetomidine 2 µg/kg intranasal 40 min before going to surgery

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|  |   |
|--|---|
| Investigational medicinal product name | Dexmedetomidine   |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Concentrate and solvent for solution for injection/infusion |
| Routes of administration               | Intranasal use  |

Dosage and administration details:

Dexmedetomidine, 100 µg/ml, 2 µg/kg, 0.2 ml/kg (0.02 ml/kg) was given intranasally with a mucosal atomizing device (

<https://www.teleflex.com/emea/en/product-areas/anaesthesia/atomization/mad-nasal-atomization-device/index.html>) 40 min before going to surgery

| <b>Number of subjects in period 1</b> | CLO group | MID group | DEX group |
|---------------------------------------|-----------|-----------|-----------|
| Started                               | 30        | 30        | 30        |
| Completed                             | 26        | 27        | 30        |
| Not completed                         | 4         | 3         | 0         |
| Refused to take IMP                   | 3         | 3         | -         |
| Protocol deviation                    | 1         | -         | -         |

## Baseline characteristics

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Perioperative period |
|-----------------------|----------------------|

Reporting group description: -

| Reporting group values                                | Perioperative period | Total |  |
|---|----------------------|-------|--|
| Number of subjects                                    | 90                   | 90    |  |
| Age categorical                                       |                      |       |  |
| Units: Subjects                                       |                      |       |  |
| In utero  | 0                    | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                    | 0     |  |
| Newborns (0-27 days)                                  | 0                    | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0                    | 0     |  |
| Children (2-11 years)                                 | 90                   | 90    |  |
| Adolescents (12-17 years)                             | 0                    | 0     |  |
| Adults (18-64 years)                                  | 0                    | 0     |  |
| From 65-84 years                                      | 0                    | 0     |  |
| 85 years and over                                     | 0                    | 0     |  |
| Gender categorical                                    |                      |       |  |
| Units: Subjects                                       |                      |       |  |
| Female  | 36                   | 36    |  |
| Male  | 54                   | 54    |  |

## End points

### End points reporting groups

|   |           |
|---|-----------|
| Reporting group title   | CLO group |
| Reporting group description:<br>Children who received clonidine 4 µg/kg oral solution 60 min before going to surgery    |           |
| Reporting group title   | MID group |
| Reporting group description:<br>Children who received midazolam 0.5mg/kg oral solution 40 min before going to surgery   |           |
| Reporting group title   | DEX group |
| Reporting group description:<br>Children who received dexmedetomidine 2 µg/kg intranasal 40 min before going to surgery |           |

### Primary: Preoperative anxiety

|  |                      |
|--|----------------------|
| End point title  | Preoperative anxiety |
| End point description:                                     |                      |
| End point type   | Primary              |
| End point timeframe:<br>Baseline<br>Anesthesia preparation |                      |

| End point values              | CLO group       | MID group       | DEX group       |  |
|-------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type            | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed   | 27              | 27              | 30              |  |
| Units: mYPAS                  |                 |                 |                 |  |
| median (full range (min-max)) | 0 (-8 to 67)    | 0 (-13 to 77)   | 0 (-13 to 63)   |  |

|                            |                              |
|----------------------------|------------------------------|
| Attachments (see zip file) | mYPAS/Figure 3 mYPAS NEW.pdf |
|----------------------------|------------------------------|

### Statistical analyses

|  |                                   |
|--|-----------------------------------|
| Statistical analysis title   | Effect on mYPAS                   |
| Statistical analysis description:<br>Comparing the change in mYPAS from baseline until the child is asleep after three different premedications.<br>The table and comparisons are shown in Table 2 in the published paper<br>( <a href="https://doi.dx.org/10.1111/pan.14279">https://doi.dx.org/10.1111/pan.14279</a> ) |                                   |
| Comparison groups  | CLO group v MID group v DEX group |

|   |                        |
|---|------------------------|
| Number of subjects included in analysis | 84                     |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | equivalence            |
| P-value                                 | = 0.036 <sup>[1]</sup> |
| Method                                  | Kruskal-wallis         |

Notes:

[1] - Comparing the differences in mYPAS at baseline and during anesthesia preparation.

## Secondary: Behavioral distress scale

|                        |                           |
|------------------------|---------------------------|
| End point title        | Behavioral distress scale |
| End point description: |                           |
| End point type         | Secondary                 |
| End point timeframe:   |                           |
| 60 min                 |                           |

| End point values              | CLO group       | MID group       | DEX group       |  |
|-------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type            | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed   | 27              | 27              | 30              |  |
| Units: Points                 |                 |                 |                 |  |
| median (full range (min-max)) | 1 (0 to 3)      | 1 (1 to 3)      | 1 (0 to 6)      |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title  | Effect on distress at Peripheral cannula insertion |
| Statistical analysis description:   |  |
| Behavioral distress scale was assessed at insertion of peripheral cannula |  |
| Comparison groups   | CLO group v MID group v DEX group                  |
| Number of subjects included in analysis                                   | 84   |
| Analysis specification  | Pre-specified                                      |
| Analysis type   | equivalence  |
| P-value   | = 0.173 <sup>[2]</sup>                             |
| Method  | Kruskal-wallis                                     |

Notes:

[2] - Non significant, i.e. no differences between groups

## Secondary: Induction compliance checklist

|  |                                |
|--|--------------------------------|
| End point title                        | Induction compliance checklist |
| End point description:                 |                                |
| The Childs compliance during induction |                                |
| End point type                         | Secondary                      |
| End point timeframe:                   |                                |
| During induction of anesthesia         |                                |



| End point values              | CLO group       | MID group       | DEX group       |  |
|-------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type            | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed   | 27              | 27              | 30              |  |
| Units: points                 |                 |                 |                 |  |
| median (full range (min-max)) | 0 (0 to 7)      | 0 (0 to 5)      | 0 (0 to 7)      |  |

### Statistical analyses

| Statistical analysis title              | ICC                               |
|---|-----------------------------------|
| Comparison groups                       | CLO group v MID group v DEX group |
| Number of subjects included in analysis | 84                                |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | equivalence                       |
| P-value                                 | = 0.871                           |
| Method                                  | Kruskal-wallis                    |

### Secondary: Sedation level Anesthesia preparation

|                           |                                       |
|---------------------------|---------------------------------------|
| End point title           | Sedation level Anesthesia preparation |
| End point description:    |                                       |
| End point type            | Secondary                             |
| End point timeframe:      |                                       |
| at Anesthesia preparation |                                       |

| End point values              | CLO group       | MID group       | DEX group       |  |
|-------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type            | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed   | 27              | 27              | 30              |  |
| Units: RSS                    |                 |                 |                 |  |
| median (full range (min-max)) | 3 (2 to 5)      | 2 (2 to 3)      | 4 (2 to 5)      |  |

### Statistical analyses

| Statistical analysis title | RSS at anesthesia preparation     |
|----------------------------|-----------------------------------|
| Comparison groups          | CLO group v DEX group v MID group |

|   |                |
|---|----------------|
| Number of subjects included in analysis | 84             |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | equivalence    |
| P-value                                 | < 0.001        |
| Method                                  | Kruskal-wallis |

## Secondary: Time to recover from anesthesia and surgery

|  |   |
|--|---|
| End point title  | Time to recover from anesthesia and surgery |
| End point description:<br>Time to recover from anaesthesia and surgery defined as the time from arrival at the PACU until the criteria of discharge from PACU was reached using the Post Anesthesia Scoring System (PADSS) |   |
| End point type   | Secondary                                   |
| End point timeframe:<br>First few hours after anesthesia   |   |

| End point values              | CLO group       | MID group       | DEX group       |  |
|-------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type            | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed   | 26              | 26              | 30              |  |
| Units: minutes                |                 |                 |                 |  |
| median (full range (min-max)) | 90 (38 to 162)  | 76 (45 to 150)  | 105 (60 to 325) |  |

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title  | Time until discharge criteria fulfilled |
| Statistical analysis description:<br>Kruskal-Wallis for the time until the discharge criteria were fulfilled, comparing the three arms. |   |
| Comparison groups   | CLO group v MID group v DEX group       |
| Number of subjects included in analysis   | 82                                      |
| Analysis specification  | Pre-specified                           |
| Analysis type   | equivalence                             |
| P-value   | = 0.211 <sup>[3]</sup>                  |
| Method  | Kruskal-wallis                          |

Notes:

[3] - No difference detected in time to full recovery from anesthesia between the groups

## Secondary: Emergence delirium

|  |                    |
|--|--------------------|
| End point title  | Emergence delirium |
| End point description:<br>PAED score ≥10p  |                    |
| End point type   | Secondary          |
| End point timeframe:<br>The time period at the postoperative ward until being discharged |                    |

| <b>End point values</b>     | CLO group       | MID group       | DEX group       |  |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type          | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed | 26              | 26              | 30              |  |
| Units: PAED > 10p           | 3               | 8               | 1               |  |

## Statistical analyses

| <b>Statistical analysis title</b>                               | Emergence delirium                |
|---|-----------------------------------|
| Statistical analysis description:                               |                                   |
| Emergence delirium at any timepoint, defined as PAES score >10p |                                   |
| Comparison groups   | CLO group v MID group v DEX group |
| Number of subjects included in analysis                         | 82                                |
| Analysis specification  | Pre-specified                     |
| Analysis type   | equivalence                       |
| P-value   | = 0.013 <sup>[4]</sup>            |
| Method  | Chi-squared                       |

Notes:

[4] - The three premedications are likely to cause different proportions of children with emergence delirium after premedication + anesthesia with total intravenous anesthesia (propofol + remifentanyl)

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The full trial period

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 25 |
|--------------------|----|

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | CLO group |
|-----------------------|-----------|

Reporting group description:

Children who received clonidine 4 µg/kg oral solution 60 min before surgery

|                       |           |
|-----------------------|-----------|
| Reporting group title | MID group |
|-----------------------|-----------|

Reporting group description:

Children who received midazolam 0.5mg/kg oral solution 40 min before surgery

|                       |           |
|-----------------------|-----------|
| Reporting group title | DEX group |
|-----------------------|-----------|

Reporting group description:

Children who received dexmedetomidine 2 µg/kg intranasal 40 min before surgery

| Serious adverse events                            | CLO group  | MID group      | DEX group      |
|---|--|----------------|----------------|
| Total subjects affected by serious adverse events |  |                |                |
| subjects affected / exposed                       | 0 / 27 (0.00%)   | 1 / 27 (3.70%) | 0 / 30 (0.00%) |
| number of deaths (all causes)                     | 0  | 0              | 0              |
| number of deaths resulting from adverse events    |  |                |                |
| Nervous system disorders                          |  |                |                |
| Surgical failure                                  | Additional description: During adenectomy unexpected liquor leak. The patient was referred to a university hospital for investigation and further treatment. It was considered a congenital malformation and completely unrelated to IMP or the surgeon. |                |                |
| subjects affected / exposed                       | 0 / 27 (0.00%)   | 1 / 27 (3.70%) | 0 / 30 (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          |

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

| Non-serious adverse events                            | CLO group       | MID group       | DEX group       |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by non-serious adverse events |                 |                 |                 |
| subjects affected / exposed                           | 3 / 27 (11.11%) | 9 / 27 (33.33%) | 6 / 30 (20.00%) |
| Cardiac disorders                                     |                 |                 |                 |

|   |  |                 |                 |
|---|--|-----------------|-----------------|
| Bradycardia<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Heart frequency                                |                 |                 |
|   | 2 / 27 (7.41%)   | 0 / 27 (0.00%)  | 0 / 30 (0.00%)  |
|   | 2  | 0               | 0               |
| Nervous system disorders<br>Delirium<br>subjects affected / exposed<br>occurrences (all)                            | Additional description: Postoperative emergence delirium               |                 |                 |
|   | 0 / 27 (0.00%)   | 3 / 27 (11.11%) | 0 / 30 (0.00%)  |
|   | 0  | 3               | 0               |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)                            | Additional description: Postoperative nausea and/or vomiting           |                 |                 |
|   | 0 / 27 (0.00%)   | 1 / 27 (3.70%)  | 3 / 30 (10.00%) |
|   | 0  | 1               | 3               |
| Respiratory, thoracic and mediastinal disorders<br>Laryngospasm<br>subjects affected / exposed<br>occurrences (all) | 1 / 27 (3.70%)   | 4 / 27 (14.81%) | 2 / 30 (6.67%)  |
|   | 1  | 4               | 2               |
|   | Additional description: small venous bleeding from the site of surgery |                 |                 |
|   | 0 / 27 (0.00%)   | 0 / 27 (0.00%)  | 1 / 30 (3.33%)  |
|   | 0  | 0               | 1               |
|   | 0 / 27 (0.00%)   | 1 / 27 (3.70%)  | 0 / 30 (0.00%)  |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all)              | Additional description: General pruritus for two weeks after surgery   |                 |                 |
|   | 0 / 27 (0.00%)   | 1 / 27 (3.70%)  | 0 / 30 (0.00%)  |
|   | 0  | 1               | 0               |

## 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.

An interim analysis was performed after 90 included participants without breaking the code. The variance within the groups in the primary objective was smaller than expected, and the intended power had been reached. Thus the study was closed.

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34403548>

<http://www.ncbi.nlm.nih.gov/pubmed/36604221>

<http://www.ncbi.nlm.nih.gov/pubmed/37528645>