



## Clinical trial results:

## Ethanol submandibular duct ligation for drooling in children with neurodisabilities

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2021-004057-23  |
| Trial protocol           | NL              |
| Global end of trial date | 31 January 2025 |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 14 May 2025  |
| First version publication date | 14 May 2025  |

### Trial information

#### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | 2021-12945 |
|-----------------------|------------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Radboudumc  |
| Sponsor organisation address | Geert Grooteplein Zuid 10, Nijmegen, Netherlands, 6525 GA   |
| Public contact               | Department of Otorhinolaryngology, Radboudumc, 0031 617377830, <a href="mailto:stijn.bekkers@radboudumc.nl">stijn.bekkers@radboudumc.nl</a> |
| Scientific contact           | dr. Stijn Bekkers, Radboudumc, 0031 617377830, <a href="mailto:stijn.bekkers@radboudumc.nl">stijn.bekkers@radboudumc.nl</a>                 |

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                       | 31 March 2025   |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 31 January 2025 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 31 January 2025 |
| Was the trial ended prematurely?                     | No              |

Notes:

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## General information about the trial

Main objective of the trial:

To evaluate the feasibility of submandibular duct ligation right after intraductal ethanol infusion into the submandibular salivary gland

Protection of trial subjects:

In accordance to section 10, subsection 4, of the WMO, the investigator will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The investigator will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

All participants and/or their caregivers provided informed consent for participation in this study. Participants were able to step out of the study at any given moment.

An insurance for subjects participating in medical research in the Radboudumc, that falls within the scope of the WMO, is available in accordance with the legal requirements of article 7 of the WMO and Medical Research (Human Subjects) Compulsory Insurance Decree of 23 June 2003.

Background therapy:

The ethanol-SDL surgery was performed in a controlled setting under strict monitoring of the Medical Ethics Committee. All interventions were performed between 2021-2024 by the same surgeon, with 25 years of experience with submandibular gland surgery. A radiologist and pediatric surgeon with specific expertise in head and neck sclerotherapy were present during the whole procedure for potential consultation.

Surgery

The intervention was performed under general anesthesia. To prevent excessive post-operative swelling, patients received 1,5 mg / kilogram Di-Adreson-F aquosum per-operatively. Patients received 30mg / kilogram of cefazoline intravenously before the procedure. The floor of the mouth was infiltrated with 1% lidocaine with 1:100.000 epinephrine and incised parallel to the frenulum. The duct was identified, a suture was placed in the surrounding tissue to apply traction, and the duct was dissected for 1 cm to expose the ductal lumen. A 0.025-inch flexible cannula was placed inside the lumen and fixated with a suture. Dehydrated ethanol (EtOH) 96% was diluted with water-soluble contrast (Iomeron 300) in a ratio of 4:1, and 2-4ml of the solution (EtOH – Iomeron 300) was injected into each of the two submandibular ducts under digital subtraction sialography to assess the required injection volume and control for extravasation from the gland capsule. The duct was clipped with two vascular clips after retraction of the canula. A suction tube was present for retrograde leakage if necessary. The sublingual incision was closed with absorbable sutures. A schematic overview of the procedure was illustrated in figure 1.

Post-operative care

Patients were admitted for one-night post-operatively, and all patients received 500/125mg amoxicillin/clavulanic acid for 7 days and 1000mg paracetamol and 25mg diclofenac for 5 days post-operatively.

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 26 July 2022 |
| 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 | Netherlands: 5 |
| Worldwide total number of subjects   | 5              |
| EEA total number of subjects         | 5              |

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)                     | 1 |
| Adolescents (12-17 years)                 | 3 |
| Adults (18-64 years)                      | 1 |
| From 65 to 84 years                       | 0 |
| 85 years and over                         | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Participants were selected from the intake consultation at the Saliva Control Clinic of the Radboud University Medical Center based on the in- and exclusion criteria, as stated in the manuscript. All participants and/or their caregivers provided written informed consent.

### Pre-assignment

Screening details:

Inclusion criteria

- Moderate to severe drooling
- Aged  $\geq 10$  at time of surgery
- Contra-indication for SMDR/rejection towards SMDR

Exclusion criteria:

- Progressive neurological disease
- Medical history of salivary gland abnormalities
- prior submandibular gland surgery
- Contraindication for surgery or anesthesia
- Other current drool treatment

### Period 1

|                              |                |
|------------------------------|----------------|
| Period 1 title               | Baseline       |
| Is this the baseline period? | Yes            |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

Blinding implementation details:

N.A.

### Arms

|           |                         |
|-----------|-------------------------|
| Arm title | Ethanol 2-duct ligation |
|-----------|-------------------------|

Arm description:

Participants received the ethanol 2-duct ligation surgery

|  |                                    |
|--|------------------------------------|
| Arm type                               | Experimental                       |
| Investigational medicinal product name | Ethanol                            |
| Investigational medicinal product code |                                    |
| Other name                             |                                    |
| Pharmaceutical forms                   | Solution for solution for infusion |
| Routes of administration               | Oral use                           |

Dosage and administration details:

Dehydrated ethanol (EtOH) 96% is diluted with water-soluble contrast (Iomeron 300) in ratio 4:1 and an estimated 2-3 mL of the solution (EtOH – Iomeron 300) is injected into the duct under digital subtraction sialography (DSS) in order to control for extravasation from the gland capsule. The maximum amount of Ethanol 96% is 4 mL per gland.

|                                       |                         |
|---------------------------------------|-------------------------|
| <b>Number of subjects in period 1</b> | Ethanol 2-duct ligation |
| Started                               | 5                       |
| Completed                             | 5                       |

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**Period 2**

|                              |                      |
|------------------------------|----------------------|
| Period 2 title               | 8 weeks post-surgery |
| Is this the baseline period? | No                   |
| Allocation method            | Not applicable       |
| Blinding used                | Not blinded          |

Blinding implementation details:

N.A.

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**Arms**

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | Surgery arm |
|------------------|-------------|

Arm description:

Ethanol 2-duct ligation

|  |                                    |
|--|------------------------------------|
| Arm type                               | Experimental                       |
| Investigational medicinal product name | Ethanol                            |
| Investigational medicinal product code |                                    |
| Other name                             |                                    |
| Pharmaceutical forms                   | Solution for solution for infusion |
| Routes of administration               | Oral use                           |

Dosage and administration details:

Dehydrated ethanol (EtOH) 96% is diluted with water-soluble contrast (Iomeron 300) in ratio 4:1 and an estimated 2-3 mL of the solution (EtOH – Iomeron 300) is injected into the duct under digital subtraction sialography (DSS) in order to control for extravasation from the gland capsule. The maximum amount of Ethanol 96% is 4 mL per gland.

|                                       |             |
|---------------------------------------|-------------|
| <b>Number of subjects in period 2</b> | Surgery arm |
| Started                               | 5           |
| Completed                             | 5           |

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**Period 3**

|                              |                       |
|------------------------------|-----------------------|
| Period 3 title               | 32 weeks post-surgery |
| Is this the baseline period? | No                    |
| Allocation method            | Not applicable        |
| Blinding used                | Not blinded           |

Blinding implementation details:

N.A.

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**Arms**

|  |                                    |
|--|------------------------------------|
| <b>Arm title</b>                       | Surgery arm                        |
| Arm description:                       |                                    |
| Ethanol 2-duct ligation                |                                    |
| Arm type                               | Experimental                       |
| Investigational medicinal product name | Ethanol                            |
| Investigational medicinal product code |                                    |
| Other name                             |                                    |
| Pharmaceutical forms                   | Solution for solution for infusion |
| Routes of administration               | Oral use                           |

Dosage and administration details:

Dehydrated ethanol (EtOH) 96% is diluted with water-soluble contrast (Iomeron 300) in ratio 4:1 and an estimated 2-3 mL of the solution (EtOH – Iomeron 300) is injected into the duct under digital subtraction sialography (DSS) in order to control for extravasation from the gland capsule. The maximum amount of Ethanol 96% is 4 mL per gland.

|                                       |             |
|---------------------------------------|-------------|
| <b>Number of subjects in period 3</b> | Surgery arm |
| Started                               | 5           |
| Completed                             | 5           |

## Baseline characteristics

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | Baseline |
|-----------------------|----------|

Reporting group description: -

| Reporting group values                                | Baseline | Total |  |
|---|----------|-------|--|
| Number of subjects                                    | 5        | 5     |  |
| 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)                                 | 1        | 1     |  |
| Adolescents (12-17 years)                             | 3        | 3     |  |
| Adults (18-64 years)                                  | 1        | 1     |  |
| From 65-84 years                                      | 0        | 0     |  |
| 85 years and over                                     | 0        | 0     |  |
| Age continuous  |          |       |  |
| Units: years  |          |       |  |
| median  | 14       |       |  |
| inter-quartile range (Q1-Q3)                          | 11 to 18 | -     |  |
| Gender categorical                                    |          |       |  |
| Units: Subjects                                       |          |       |  |
| Female  | 2        | 2     |  |
| Male  | 3        | 3     |  |

## End points

### End points reporting groups

|   |                         |
|---|-------------------------|
| Reporting group title   | Ethanol 2-duct ligation |
| Reporting group description:<br>Participants received the ethanol 2-duct ligation surgery |                         |
| Reporting group title   | Surgery arm             |
| Reporting group description:<br>Ethanol 2-duct ligation                                   |                         |
| Reporting group title   | Surgery arm             |
| Reporting group description:<br>Ethanol 2-duct ligation                                   |                         |

### Primary: Feasibility

|   |                            |
|---|----------------------------|
| End point title                               | Feasibility <sup>[1]</sup> |
| End point description:                        |                            |
| End point type                                | Primary                    |
| End point timeframe:<br>32 weeks post-surgery |                            |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were performed on the descriptive statistics, as it was only a registration of the number of completed surgeries, and this study only included 1 arm, with 5 participants.

| End point values            | Ethanol 2-duct ligation | Surgery arm     |  |  |
|-----------------------------|-------------------------|-----------------|--|--|
| Subject group type          | Reporting group         | Reporting group |  |  |
| Number of subjects analysed | 5                       | 5               |  |  |
| Units: Surgery completion   | 5                       | 5               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Safety

|   |                       |
|---|-----------------------|
| End point title                               | Safety <sup>[2]</sup> |
| End point description:                        |                       |
| End point type                                | Primary               |
| End point timeframe:<br>32 weeks post-surgery |                       |



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Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were performed on the descriptive statistics, as it was only a registration of the number of serious adverse events, and this study only included 1 arm, with 5 participants.

| <b>End point values</b>     | Ethanol 2-duct<br>ligation | Surgery arm     | Surgery arm     |  |
|-----------------------------|----------------------------|-----------------|-----------------|--|
| Subject group type          | Reporting group            | Reporting group | Reporting group |  |
| Number of subjects analysed | 5                          | 5               | 5               |  |
| Units: Adverse Events       | 0                          | 0               | 0               |  |

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

32 weeks post-surgery

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 28 |
|--------------------|----|

### Reporting groups

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Ethanol 2-duct ligation |
|-----------------------|-------------------------|

Reporting group description:

Participants received the ethanol 2-duct ligation surgery

| Serious adverse events                            | Ethanol 2-duct ligation |  |  |
|---|-------------------------|--|--|
| Total subjects affected by serious adverse events |                         |  |  |
| subjects affected / exposed                       | 0 / 5 (0.00%)           |  |  |
| number of deaths (all causes)                     | 0                       |  |  |
| number of deaths resulting from adverse events    | 0                       |  |  |

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

| Non-serious adverse events                            | Ethanol 2-duct ligation  |  |  |
|---|--|--|--|
| Total subjects affected by non-serious adverse events |  |  |  |
| subjects affected / exposed                           | 2 / 5 (40.00%)   |  |  |
| Gastrointestinal disorders                            |  |  |  |
| gastro-enteritis                                      | Additional description: Hospital admission approximately 32-weeks post-surgery with 3 days of gastro-enteritis with fever. |  |  |
| subjects affected / exposed <sup>[1]</sup>            | 1 / 1 (100.00%)  |  |  |
| occurrences (all)                                     | 1  |  |  |
| Skin and subcutaneous tissue disorders                |  |  |  |
| Allergic skin reaction                                | Additional description: Mild allergic skin reaction to the antibiotic medication post-surgery                              |  |  |
| subjects affected / exposed <sup>[2]</sup>            | 1 / 1 (100.00%)  |  |  |
| occurrences (all)                                     | 1  |  |  |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The individual participant presented with a gastro-enteritis at 32-weeks post-surgery. This was not related to the exposure to the medical product. No other participants were exposed to gastro-

enteritis.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This was the only participant who appeared to have an allergic response to the antibiotic treatment. This was not directly related to the exposure to the medical product. No other participants had a similar allergic response to antibiotics.

## **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