# Clinical trial results:
# Double-blind randomized clinical trial to compare presurgery anxiolysis in children treated with hydroxyzine versus non-pharmacological intervention (distractoria technique clown).

## Summary

| | |
|---|---|
| EudraCT number | 2016-002890-37 |
| Trial protocol | ES |
| Global end of trial date | 21 February 2021 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 25 May 2022 |
| First version publication date | 25 May 2022 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 1 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03324828 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Esther Aleo Lujan |
| Sponsor organisation address | profesor martin lagos s/n, Madrid, Spain, 28040 |
| Public contact | Servicio de Pediatría Hospital Clinico San Carlos, Esther Aleo Lujan, +34 913303000, fibucicec.hcsc@salud.madrid.org |
| Scientific contact | Servicio de Pediatría Hospital Clinico San Carlos, Esther Aleo Lujan, +34 913303000, fibucicec.hcsc@salud.madrid.org |

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 | 31 May 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 21 February 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 21 February 2021 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess whether the association of pharmacological measures (hydroxyzine) and not pharmacological (distraction by clowns) decreases preoperative anxiety (POA) for children who will be undergoing outpatient surgery.

Protection of trial subjects:

The study was approved by the Clinical Research Ethics Committee of the hospital. The confidentiality of subject data was always maintained in
accordance with current legislation. Written informed consent was obtained before any intervention from all subjects, legal surrogates, parents, or legal guardians for minor subjects.
This study was carried out following international ethical recommendations for conducting human research and clinical trials contained in the latest revision of the Declaration of Helsinki as well as those established in the Good Clinical Practice Guidelines and current legislation. All subjects were supervised by qualified medical personnel during their participation in the study.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 23 October 2018 |
| 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 | Spain: 165 |
| Worldwide total number of subjects | 165 |
| EEA total number of subjects | 165 |

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) | 128 |
| Adolescents (12-17 years) | 37 |

| | |
|---|---|
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

We studied 165 patients with ages between 2 and 16 years (mean 7.4, SD 4.2). 127 were boys, and 41 were girls. The declaration of the COVID-19 global pandemic forced the premature ending of the study, and thus, the objective sample size was only reached in groups 1 (hydroxyzine) and 2 (placebo).

### Period 1

| | |
|---|---|
| Period 1 title | Time-Point 0 (M0) (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Group 1 |

Arm description:

Pharmacological intervention (oral hydroxyzine 2 mg/kg masked with 5 ml of juice, administered at least 30 min prior to surgery) plus standard management consisting of parental accompaniment during the preoperative period, postanesthesia recovery area, and up to hospital discharge

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

Dosage and administration details:

mg/kg masked with 5 ml of juice, administered at least 30 min prior to surgery

| | |
|---|---|
| **Arm title** | Group 2 |

Arm description:

Standard management

| | |
|---|---|
| Arm type | No intervention |

No investigational medicinal product assigned in this arm

| | |
|---|---|
| **Arm title** | Group 3 |

Arm description:

Standard management + Dr. Sonrisas + oral hydroxyzine

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

Dosage and administration details:

2 mg/kg masked with 5 ml of juice, administered at least 30 min prior to surgery

| | |
|---|---|
| **Arm title** | Group 4 |

Arm description:

Standard management + Dr. Sonrisas

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

Dosage and administration details:

5 ml of juice, administered at least 30 min prior to surgery

| **Number of subjects in period 1** | Group 1 | Group 2 | Group 3 |
|---|---|---|---|
| Started | 59 | 52 | 25 |
| Completed | 53 | 48 | 24 |
| Not completed | 6 | 4 | 1 |
| Consent withdrawn by subject | 1 | - | - |
| Screening failure | 3 | 3 | - |
| Lost to follow-up | 1 | 1 | - |
| discontinuation | 1 | - | 1 |

| **Number of subjects in period 1** | Group 4 |
|---|---|
| Started | 29 |
| Completed | 27 |
| Not completed | 2 |
| Consent withdrawn by subject | - |
| Screening failure | 2 |
| Lost to follow-up | - |
| discontinuation | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Group 1 |
| Reporting group description: | |
| Pharmacological intervention (oral hydroxyzine 2 mg/kg masked with 5 ml of juice, administered at least 30 min prior to surgery) plus standard management consisting of parental accompaniment during the preoperative period, postanesthesia recovery area, and up to hospital discharge | |
| Reporting group title | Group 2 |
| Reporting group description: | |
| Standard management | |
| Reporting group title | Group 3 |
| Reporting group description: | |
| Standard management + Dr. Sonrisas + oral hydroxyzine | |
| Reporting group title | Group 4 |
| Reporting group description: | |
| Standard management + Dr. Sonrisas | |

| Reporting group values | Group 1 | Group 2 | Group 3 |
|---|---|---|---|
| Number of subjects | 59 | 52 | 25 |
| Age categorical | | | |
| Age (years) Mean ± SD | | | |
| Units: Subjects | | | |
| Children (2-11 years) | 46 | 41 | 19 |
| Adolescents (12-17 years) | 13 | 11 | 6 |
| Age continuous | | | |
| Age (years) Mean ± SD | | | |
| Units: years | | | |
| arithmetic mean | 7.7 | 8.0 | 7.7 |
| standard deviation | ± 4.1 | ± 4.3 | ± 4.1 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 53 | 40 | 19 |
| Male | 6 | 12 | 6 |

| Reporting group values | Group 4 | Total | |
|---|---|---|---|
| Number of subjects | 29 | 165 | |
| Age categorical | | | |
| Age (years) Mean ± SD | | | |
| Units: Subjects | | | |
| Children (2-11 years) | 22 | 128 | |
| Adolescents (12-17 years) | 7 | 37 | |
| Age continuous | | | |
| Age (years) Mean ± SD | | | |
| Units: years | | | |
| arithmetic mean | 6.4 | | |
| standard deviation | ± 3.3 | - | |

| Gender categorical<br>Units: Subjects | | | |
|---|---|---|---|
| Female | 21 | 133 | |
| Male | 8 | 32 | |

## End points

| End points reporting groups | |
|---|---|
| Reporting group title | Group 1 |
| Reporting group description: | |
| Pharmacological intervention (oral hydroxyzine 2 mg/kg masked with 5 ml of juice, administered at least 30 min prior to surgery) plus standard management consisting of parental accompaniment during the preoperative period, postanesthesia recovery area, and up to hospital discharge | |
| Reporting group title | Group 2 |
| Reporting group description: | |
| Standard management | |
| Reporting group title | Group 3 |
| Reporting group description: | |
| Standard management + Dr. Sonrisas + oral hydroxyzine | |
| Reporting group title | Group 4 |
| Reporting group description: | |
| Standard management + Dr. Sonrisas | |

| Primary: m-YPAS at the time of anaesthetic induction | |
|---|---|
| End point title | m-YPAS at the time of anaesthetic induction |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| M3: at the time of anaesthetic induction | |

| End point values | Group 1 | Group 2 | Group 3 | Group 4 |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 53 | 48 | 24 | 27 |
| Units: m-YPAS scale | | | | |
| geometric mean (standard deviation) | 39.2 (± 27.9) | 37 (± 26.1) | 34.7 (± 25.5) | 32.4 (± 20.5) |

### Statistical analyses

| Statistical analysis title | ANOVA |
|---|---|
| Comparison groups | Group 1 v Group 2 v Group 3 v Group 4 |
| Number of subjects included in analysis | 152 |
| Analysis specification | Post-hoc |
| Analysis type | equivalence |
| P-value | ≤ 0.05 |
| Method | ANOVA |

## Secondary: ICC values

| End point title | ICC values |
|---|---|

End point description:

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

End point timeframe:

M3: at the time of anaesthetic induction

| End point values | Group 1 | Group 2 | Group 3 | Group 4 |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 53 | 48 | 24 | 27 |
| Units: ICC values | | | | |
| geometric mean (standard deviation) | 1.8 (± 3.4) | 1.5 (± 3) | 1.2 (± 2.4) | 1.5 (± 3.0) |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information[1] | |
|---|---|
| Timeframe for reporting adverse events:<br>throughout the study | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 24 |

Frequency threshold for reporting non-serious adverse events: 0 %

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: There are no non-serious adverse events recorded for these results.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 22 August 2017 | Elimination STAI/SCAP anxiety scale.<br>Exclusion criteria actualization. |
| 01 November 2017 | Selection Criteria actualization. |
| 12 December 2017 | Criteria selection actualization |
| 10 August 2018 | Data proteccion actualization |
| 10 April 2019 | Inclusion an analysis of ACTH and cortisol level |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported