# Clinical trial results:
# Phase IV study comparing the efficacy and safety of an alcohol-free formulation of 0.15% benzydamine hydrochloride spray and benzydamine hydrochloride 3mg lozenges in paediatric patients (6-12 years) with sore throat.

## Summary

| | |
|---|---|
| EudraCT number | 2022-003285-20 |
| Trial protocol | HU BG |
| Global end of trial date | 18 January 2024 |
| **Results information** | |
| Result version number | v1 (current) |
| This version publication date | 16 April 2025 |
| First version publication date | 16 April 2025 |

## Trial information

| **Trial identification** | |
|---|---|
| Sponsor protocol code | 030(Z)MD22061 |
| **Additional study identifiers** | |
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

| **Sponsors** | |
|---|---|
| Sponsor organisation name | Angelini Pharma S.p.A. |
| Sponsor organisation address | Via Amelia 70, Roma, Italy, 00181 |
| Public contact | Study Manager, Angelini Pharma S.p.A., 0039 3472274815, martina.barcaroli@angelinipharma.com |
| Scientific contact | Study Manager, Angelini Pharma S.p.A., 0039 3472274815, martina.barcaroli@angelinipharma.com |

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? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 18 January 2024 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 18 January 2024 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to assess the local analgesic effect of benzydamine hydrochloride (spray or lozenges) in reducing sore throat pain at T15 min after a single dose administration to paediatric patients.

Protection of trial subjects:

This trial was conducted in accordance with the study protocol, GCPs, Declaration of Helsinki (including up-to-date versions) and applicable regulatory requirements.
The child participated the study only after parents/legal guardian signature of the ICF and GDPR Consent and (whenever possible) by giving his/her own assent. The Investigator asked to confirm the occurrence of the parents/legal guardian’s consent (and child's assent,) to participate to the study and to process personal data by signing the relevant ICF and GDPR Consent , respectively.
Original signed versions of the ICFs, GDPR Consents and Assents availabled for monitoring and auditing visits at the investigational site.

Background therapy: -

Evidence for comparator:

The purpose of this study was generate new clinical data and update available information on the use of benzydamine in children.
The local analgesic effect in reducing throat pain provided by a single application of benzydamine hydrochloride 3 mg lozenges and benzydamine hydrochloride 0.15 % spray was investigated.

| | |
|---|---|
| Actual start date of recruitment | 16 June 2023 |
| 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 | Bulgaria: 138 |
| Country: Number of subjects enrolled | Hungary: 116 |
| Country: Number of subjects enrolled | Romania: 109 |
| Worldwide total number of subjects | 363 |
| EEA total number of subjects | 363 |

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) | 343 |
| Adolescents (12-17 years) | 20 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

A total of 363 subjects, male and female pediatric patients (aged 6-12 years) with sore throat symptoms were enrolled, 185 and 178 in the spray and lozenges groups, respectively.

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 363 |
| Number of subjects completed | 363 |

### Period 1

| | |
|---|---|
| Period 1 title | Overall (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Test drug: 0.15% Benzydamine hydrochloride spray |

Arm description:

The first dose (4 puffs) was administered at the site by the investigator, the subject and parents/legal guardian was instructed to administer the dose of 4 puffs from 2 to 6 times a day until sore throat disappearance or for a maximum of 7 days.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Benzydamine hydrochloride 0.15%, oromucosal spray |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oromucosal spray |
| Routes of administration | Oromucosal use |

Dosage and administration details:

The dose of 4 puffs from 2 to 6 times a day until sore throat disappearance or for a maximum of 7 days. 1 puff is equivalent to 0.255mg of benzydamine hydrochloride, thus the first dose is equivalent to 1.02mg and total daily dose ranges from 2.04mg to 6.12mg benzydamine hydrochloride.

| | |
|---|---|
| **Arm title** | Test Comparator: Benzydamine hydrochloride lozenges 3mg |

Arm description:

A single 3mg lozenge of benzydamine hydrochloride was administered at the investigational site.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Lozenge of benzydamine hydrochloride |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Lozenge |
| Routes of administration | Oral use |

Dosage and administration details:

Dose: 3mg lozenge of benzydamine hydrochloride was administered. Then, parents will take the drug at home, according to the product’s relevant SmPC, 3 times a day for a maximum of 7 days from the first application

| **Number of subjects in period 1** | Test drug: 0.15% Benzydamine hydrochloride spray | Test Comparator: Benzydamine hydrochloride lozenges 3mg |
|---|---|---|
| Started | 185 | 178 |
| Completed | 185 | 178 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Overall |
|---|---|

Reporting group description: -

| Reporting group values | Overall | Total | |
|---|---|---|---|
| Number of subjects | 363 | 363 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 343 | 343 | |
| Adolescents (12-17 years) | 20 | 20 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 8.6 | | |
| standard deviation | ± 1.8 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 170 | 170 | |
| Male | 193 | 193 | |

### Subject analysis sets

| Subject analysis set title | Safety Population |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety analyses were performed on the safety population (SP), which included all randomized subjects who have taken at least one dose of the IMP.

| Subject analysis set title | m-ITT |
|---|---|
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

All randomized subjects who have taken at least one dose of the IMP and having the T15 min posttreatment efficacy assessment with the WBS score were included in the m-ITT population.

| Subject analysis set title | PP Population |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

All randomized subjects who have taken at least the first dose of the IMP and having all Day 0 (up to T45 min) WBS score evaluations, with no major protocol violations were included in the PP population

| **Reporting group values** | Safety Population | m-ITT | PP Population |
|---|---|---|---|
| Number of subjects | 363 | 362 | 347 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 343 | 342 | 328 |
| Adolescents (12-17 years) | 20 | 20 | 19 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 8.6 | 8.6 | 8.6 |
| standard deviation | ± 1.8 | ± 1.8 | ± 1.8 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 170 | 169 | 166 |
| Male | 193 | 193 | 181 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Test drug: 0.15% Benzydamine hydrochloride spray |

Reporting group description:

The first dose (4 puffs) was administered at the site by the investigator, the subject and parents/legal guardian was instructed to administer the dose of 4 puffs from 2 to 6 times a day until sore throat disappearance or for a maximum of 7 days.

| | |
|---|---|
| Reporting group title | Test Comparator: Benzydamine hydrochloride lozenges 3mg |

Reporting group description:

A single 3mg lozenge of benzydamine hydrochloride was administered at the investigational site.

| | |
|---|---|
| Subject analysis set title | Safety Population |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety analyses were performed on the safety population (SP), which included all randomized subjects who have taken at least one dose of the IMP.

| | |
|---|---|
| Subject analysis set title | m-ITT |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

All randomized subjects who have taken at least one dose of the IMP and having the T15 min posttreatment efficacy assessment with the WBS score were included in the m-ITT population.

| | |
|---|---|
| Subject analysis set title | PP Population |
| Subject analysis set type | Per protocol |

Subject analysis set description:

All randomized subjects who have taken at least the first dose of the IMP and having all Day 0 (up to T45 min) WBS score evaluations, with no major protocol violations were included in the PP population

### Primary: WBS at 15 mins

| | |
|---|---|
| End point title | WBS at 15 mins |

End point description:

The primary endpoint was the non-inferiority of the test product (defined as the difference between test and reference product 95% CI lower bound of WBS score reduction above 10%) when compared to the reference product with respect to the differences in the percentage of participants who reported a reduction of at least one face (equal to two points) in the WBS score at T15 min after the first application vs. baseline.

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

End point timeframe:

15 min

| End point values | Test drug: 0.15% Benzydamine hydrochloride spray | Test Comparator: Benzydamine hydrochloride lozenges 3mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 185 | 178 | | |
| Units: Percentage (%) | 83 | 86 | | |

## Statistical analyses

| **Statistical analysis title** | Wald 95% CI |
|---|---|
| Statistical analysis description:<br>Wald 95% CI | |
| Comparison groups | Test drug: 0.15% Benzydamine hydrochloride spray v Test Comparator: Benzydamine hydrochloride lozenges 3mg |
| Number of subjects included in analysis | 363 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Method | Wald 95% CI |
| Parameter estimate | 95% CI |
| Point estimate | -4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.6 |
| upper limit | 3.5 |

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Subjects administered with Benzydamine hydrochloride 0.5% spray | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 26.1 |

| Reporting groups | |
|---|---|
| Reporting group title | Benzydamine hydrochloride - spray |
| Reporting group description: - | |
| Reporting group title | Benzydamine hydrochloride Lozenges 3mg |
| Reporting group description: - | |

| Serious adverse events | Benzydamine hydrochloride - spray | Benzydamine hydrochloride Lozenges 3mg | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 185 (0.00%) | 0 / 178 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

Frequency threshold for reporting non-serious adverse events: 0.5 %

| Non-serious adverse events | Benzydamine hydrochloride - spray | Benzydamine hydrochloride Lozenges 3mg | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 185 (7.03%) | 7 / 178 (3.93%) | |
| Nervous system disorders | | | |
| headache | | | |
| subjects affected / exposed | 1 / 185 (0.54%) | 1 / 178 (0.56%) | |
| occurrences (all) | 1 | 1 | |
| General disorders and administration site conditions | | | |
| application site hypoaesthesia | | | |
| subjects affected / exposed | 0 / 185 (0.00%) | 1 / 178 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Fatigue | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 185 (0.00%) | 1 / 178 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 1 / 185 (0.54%) | 1 / 178 (0.56%) | |
| occurrences (all) | 1 | 1 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 185 (0.54%) | 0 / 178 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Salivary Hypersecretion | | | |
| subjects affected / exposed | 0 / 185 (0.00%) | 1 / 178 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 185 (0.54%) | 0 / 178 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tongue discomfort | | | |
| subjects affected / exposed | 0 / 185 (0.00%) | 1 / 178 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 3 / 185 (1.62%) | 0 / 178 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| cough | | | |
| subjects affected / exposed | 1 / 185 (0.54%) | 1 / 178 (0.56%) | |
| occurrences (all) | 1 | 1 | |
| dysphonia | | | |
| subjects affected / exposed | 1 / 185 (0.54%) | 0 / 178 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| nasal obstruction | | | |
| subjects affected / exposed | 0 / 185 (0.00%) | 1 / 178 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| oropharyngeal discomfort | | | |
| subjects affected / exposed | 0 / 185 (0.00%) | 1 / 178 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| productive cough | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 185 (0.54%) | 0 / 178 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| drug eruption | | | |
| subjects affected / exposed | 1 / 185 (0.54%) | 0 / 178 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| pruritus | | | |
| subjects affected / exposed | 1 / 185 (0.54%) | 0 / 178 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| myalgia | | | |
| subjects affected / exposed | 0 / 185 (0.00%) | 1 / 178 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Ear infection | | | |
| subjects affected / exposed | 1 / 185 (0.54%) | 0 / 178 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| rhinitis | | | |
| subjects affected / exposed | 1 / 185 (0.54%) | 0 / 178 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| sinusitis | | | |
| subjects affected / exposed | 0 / 185 (0.00%) | 1 / 178 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| tonsillitis bacterial | | | |
| subjects affected / exposed | 1 / 185 (0.54%) | 0 / 178 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| viral rash | | | |
| subjects affected / exposed | 1 / 185 (0.54%) | 0 / 178 (0.00%) | |
| occurrences (all) | 1 | 0 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported