# Clinical trial results:
# Efficacy and safety of the combination of ibuprofen and paracetamol versus ibuprofen in monotherapy in acute Low Back Pain (LBP)

## Summary

| | |
|---|---|
| EudraCT number | 2020-005278-86 |
| Trial protocol | IT PL |
| Global end of trial date | 05 October 2022 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 09 May 2024 |
| First version publication date | 09 May 2024 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 147(Z)WO20157 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT05222724 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Angelini Pharma S.p.A |
| Sponsor organisation address | Via Amelia 70, Rome, Italy, 00181 |
| Public contact | Martina Barcaroli, Angelini Pharma S.p.A., +39 3472274815, martina.barcaroli@angelinipharma.com |
| Scientific contact | Martina Barcaroli, Angelini Pharma S.p.A., +39 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? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 05 October 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 October 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 October 2022 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study is to assess the pain improvement in patients with uncomplicated non-specific acute low back pain after a 3-day treatment period with paracetamol/ibuprofen FDC compared to ibuprofen.

Protection of trial subjects:

The study was conducted, in compliance with the protocol, regulatory requirements, good clinical practice (GCP) (including up-to-date versions) and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.
All patients provided written informed consent to participate in the study before any study-related procedures.
The patients were given a copy of the ICF for their information. The original copy of the informed consent was kept in a confidential file in the Investigator’s site records. Patients were also informed by the Investigator of all aspects related to their personal data processing, as well as their rights on this matter.

Background therapy:

Not applicable

Evidence for comparator:

The Reference was Ibuprofen 600 mg film-coated tablets (Brufen 600 mg film-coated tablets) that is a NSAIDs effective to relieve the pain and to improve functionality in the treatment of Low Back Pain (LBP).

| | |
|---|---|
| Actual start date of recruitment | 26 October 2021 |
| 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 | Poland: 170 |
| Country: Number of subjects enrolled | Italy: 5 |
| Worldwide total number of subjects | 175 |
| EEA total number of subjects | 175 |

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) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 174 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

A total of 179 patients were enrolled and 175 of them were randomized 1:1 to one of the following two treatment groups: Group 1: paracetamol 500 mg/ibuprofen 150 mg and Group 2: ibuprofen 600 mg and 3 patients of 175 didn't assume any dose of study treatment. A total of 172 patients were treated.

### Pre-assignment

Screening details:

The Investigator assigned to patients fulfilling eligibility criteria the randomization number, by removing the upper layer of the label of the first available randomization number on the Randomization Label Form, where the assigned treatment was indicated.

### Period 1

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

Blinding implementation details:

Not applicable. This was an open-label study

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Test: Tachifene 500mg/150mg |

Arm description:

Subjects treated with the Fixed-Dose Combination (FDC) of 500 mg/ibuprofen 150 mg, two film-coated tablets (Tachifene® 500 mg/150 mg)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Paracetamol 500 mg/ ibuprofen 150 mg |
| Investigational medicinal product code | Sponsor code 147(Z) |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The patient took two tablets 3 times daily for 3 days (i.e., every 8 hours ± 1 hour) until Day 3 (± 1) according to the relevant Summary of Product Characteristics (SmPC). Tablets were swallowed without chewing. Ingestion could be helped by a small amount of water.

| | |
|---|---|
| **Arm title** | Reference: Brufen 600 mg |

Arm description:

Subjects treated with Ibuprofen 600 mg (Brufen 600 mg film-coated tablets).

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Ibuprofen 600 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The patient took one tablet of Ibuprofen 600 mg 3 times daily for 3 days (i.e., every 8 hours ± 1 hour). Tablets were swallowed without chewing. Ingestion could be helped by a small amount of water.

| **Number of subjects in period 1** | Test: Tachifene 500mg/150mg | Reference: Brufen 600 mg |
|---|---|---|
| Started | 87 | 88 |
| Completed | 82 | 85 |
| Not completed | 5 | 3 |
| Patient requests to be excluded from the study (in | - | 1 |
| Additional therapy for LBP | 1 | - |
| Lost to follow-up | 3 | - |
| Protocol deviation | 1 | 2 |

## Baseline characteristics

### Reporting groups

| | |
|---|---|
| Reporting group title | OVERAL TRIAL |

Reporting group description: -

| Reporting group values | OVERAL TRIAL | Total | |
|---|---|---|---|
| Number of subjects | 175 | 175 | |
| Age categorical | | | |
| Patients with uncomplicated and localized acute LBP or acute exacerbation of chronic LBP (not radiating below the gluteal fold), with moderate/severe pain at baseline. Minimum visual analogue scale (VAS) score ≥ 40 mm at screening visit. | | | |
| 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) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 174 | 174 | |
| From 65-84 years | 1 | 1 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Male and female patients of any ethnic origin between 18 and 64 years of age (limits included) | | | |
| Units: Subjects | | | |
| Female | 102 | 102 | |
| Male | 73 | 73 | |

### Subject analysis sets

| | |
|---|---|
| Subject analysis set title | Safety population (SP) |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The Safety Population (SP) was defined as all randomized patients who took at least one dose of the study medication.

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

Subject analysis set description:

The modified Intention-to-Treat (m-ITT) population: all randomized patients who took at least one dose of the study medication and had at least baseline (Day 0) and one post baseline evaluation on the LBP assessment. The Last Observation Carried Forward (LOCF) method was implemented as imputation scheme for missing data in the m-ITT population.

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

Subject analysis set description:

The PP population was defined as all randomized patients who took at least one dose of the study medication and had at least baseline (Day 0), Day 4 (± 1) and Day 8 (± 1) evaluations on the LBP assessment, with no major protocol violations.

| **Reporting group values** | Safety population (SP) | m-ITT population | PP Population |
|---|---|---|---|
| Number of subjects | 172 | 171 | 152 |
| Age categorical | | | |
| Patients with uncomplicated and localized acute LBP or acute exacerbation of chronic LBP (not radiating below the gluteal fold), with moderate/severe pain at baseline. Minimum visual analogue scale (VAS) score ≥ 40 mm at screening visit. | | | |
| 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) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 171 | 170 | 151 |
| From 65-84 years | 1 | 1 | 1 |
| 85 years and over | 0 | 0 | 0 |
| Gender categorical | | | |
| Male and female patients of any ethnic origin between 18 and 64 years of age (limits included) | | | |
| Units: Subjects | | | |
| Female | 100 | 99 | |
| Male | 72 | 72 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Test: Tachifene 500mg/150mg |

Reporting group description:

Subjects treated with the Fixed-Dose Combination (FDC) of 500 mg/ibuprofen 150 mg, two film-coated tablets (Tachifene® 500 mg/150 mg)

| | |
|---|---|
| Reporting group title | Reference: Brufen 600 mg |

Reporting group description:

Subjects treated with Ibuprofen 600 mg (Brufen 600 mg film-coated tablets).

| | |
|---|---|
| Subject analysis set title | Safety population (SP) |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The Safety Population (SP) was defined as all randomized patients who took at least one dose of the study medication.

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

Subject analysis set description:

The modified Intention-to-Treat (m-ITT) population: all randomized patients who took at least one dose of the study medication and had at least baseline (Day 0) and one post baseline evaluation on the LBP assessment. The Last Observation Carried Forward (LOCF) method was implemented as imputation scheme for missing data in the m-ITT population.

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

Subject analysis set description:

The PP population was defined as all randomized patients who took at least one dose of the study medication and had at least baseline (Day 0), Day 4 (± 1) and Day 8 (± 1) evaluations on the LBP assessment, with no major protocol violations.

### Primary: SPID 0-3 days

| | |
|---|---|
| End point title | SPID 0-3 days |

End point description:

The primary endpoint was the area under the pain intensity difference-versus-time curve of LBP scores up to three days of treatment (sum of the pain intensity differences [SPID] 0-3 days). The pain intensity difference was considered the difference in visual analogue scale (VAS) pain intensity between one time point and the baseline. The SPID was the sum of the average of two consecutive pain intensity differences multiplied by the time-interval between two time points.

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

End point timeframe:

0-3 days

| End point values | Test: Tachifene 500mg/150mg | Reference: Brufen 600 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 83[1] | 88[2] | | |
| Units: number | | | | |
| arithmetic mean (standard deviation) | -45.18 (± 33.01) | -40.96 (± 29.65) | | |

Notes:
[1] - Subjects beloning to m-IIT population
[2] - Subjects belonging m-ITT population

| **Attachments (see zip file)** | Additional Results (Secondary end points)/2020-005278- |
|---|---|

### Statistical analyses

| **Statistical analysis title** | ANCOVA |
|---|---|
| Statistical analysis description:<br>ANCOVA model with center and baseline as covariates | |
| Comparison groups | Test: Tachifene 500mg/150mg v Reference: Brufen 600 mg |
| Number of subjects included in analysis | 171 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1038 |
| Method | ANCOVA |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From 26 October 2021 to 5 October 2022

Adverse event reporting additional description:

The AEs are divided into two categories, based on the time of AE occurrence: Pre-treatment adverse events (PTAE) and treatment-emergent adverse events (TEAE). Only TEAE as any AE occurring or worsening after the first dose of a medicinal product are reported

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 23.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Reference: Brufen 600mg |
| Reporting group description: - | |
| Reporting group title | Test: Tachifene 500mg/150mg |
| Reporting group description: - | |

| Serious adverse events | Reference: Brufen 600mg | Test: Tachifene 500mg/150mg | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 84 (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: 2 %

| Non-serious adverse events | Reference: Brufen 600mg | Test: Tachifene 500mg/150mg | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 23 / 88 (26.14%) | 19 / 84 (22.62%) | |
| Investigations | | | |
| Aspartate | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 84 (1.19%) | |
| occurrences (all) | 0 | 1 | |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 84 (1.19%) | |
| occurrences (all) | 0 | 1 | |
| Gamma-glutamyltransferase increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 84 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urine phosphorus abnormal | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 84 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Intentional product misuse | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 84 (1.19%) | |
| occurrences (all) | 0 | 1 | |
| Medication error | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | 3 / 84 (3.57%) | |
| occurrences (all) | 2 | 3 | |
| Overdose | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 3 / 84 (3.57%) | |
| occurrences (all) | 1 | 3 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 84 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 4 / 88 (4.55%) | 0 / 84 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Migraine | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 84 (1.19%) | |
| occurrences (all) | 0 | 1 | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 2 / 84 (2.38%) | |
| occurrences (all) | 1 | 2 | |
| Blood and lymphatic system disorders | | | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 84 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 84 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---|---|---|
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 84 (1.19%) | |
| occurrences (all) | 0 | 1 | |
| Feeling cold | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 84 (1.19%) | |
| occurrences (all) | 0 | 1 | |
| Swelling face | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 84 (1.19%) | |
| occurrences (all) | 0 | 1 | |
| Eye disorders | | | |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 84 (1.19%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | 1 / 84 (1.19%) | |
| occurrences (all) | 2 | 1 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 84 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 88 (3.41%) | 1 / 84 (1.19%) | |
| occurrences (all) | 3 | 1 | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 88 (3.41%) | 0 / 84 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 84 (1.19%) | |
| occurrences (all) | 0 | 1 | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 84 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Flatulence | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 84 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---|---|---|
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 84 (1.19%) | |
| occurrences (all) | 0 | 1 | |
| Nausea | | | |
| subjects affected / exposed | 3 / 88 (3.41%) | 0 / 84 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Oesophageal discomfort | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 84 (1.19%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Sinus p | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 84 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Throat irritation | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 84 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 1 / 84 (1.19%) | |
| occurrences (all) | 1 | 1 | |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 84 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 84 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 84 (1.19%) | |
| occurrences (all) | 0 | 1 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 2 / 84 (2.38%) | |
| occurrences (all) | 1 | 2 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 0 / 88 (0.00%)<br>0 | 1 / 84 (1.19%)<br>1 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 11 March 2022 | The substantial amendment (Amendment nº 7 of 11/Mar/2022 ) was made after first patient enrolled in the study.<br>According to the opinion of the Investigators involved in the study and after a careful analysis performed by the Sponsor, a few exclusion criteria ( n. 7, 8 and 9) were better detailed for the definition of patients' eligibility. Hungary was deleted from the countries involved in the clinical study. In addition, some changes for safety reasons (related to the difficulty for patients to step up on the platform) were done to modify the procedure for patient mobility restriction assessment.<br>The description of the "PGIC scale" was aligned with the validated one effectively submitted for the study. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported