



## 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
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##### 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
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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:

## 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
<b>Arm title</b>	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  $\pm$  1 hour) until Day 3 ( $\pm$  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.

<b>Arm title</b>	Reference: Brufen 600 mg
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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  $\pm$  1 hour). Tablets were swallowed without chewing. Ingestion could be helped by a small amount of water.

<b>Number of subjects in period 1</b>	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 $\geq 40$ 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 ( $\pm 1$ ) and Day 8 ( $\pm 1$ ) 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 $\geq 40$ 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 ( $\pm 1$ ) and Day 8 ( $\pm 1$ ) 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 <sup>[1]</sup>	88 <sup>[2]</sup>		
Units: number				
arithmetic mean (standard deviation)	-45.18 ( $\pm$ 33.01)	-40.96 ( $\pm$ 29.65)		



Notes:

[1] - Subjects belonging to m-IIT population

[2] - Subjects belonging m-ITT population

<b>Attachments (see zip file)</b>	Additional Results (Secondary end points)/2020-005278-
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### Statistical analyses

<b>Statistical analysis title</b>	ANCOVA
Statistical analysis description: 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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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### Reporting groups

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

Reporting group title	Test: Tachifene 500mg/150mg
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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 occurrences (all)	1 / 88 (1.14%) 1	0 / 84 (0.00%) 0	
Urine phosphorus abnormal subjects affected / exposed occurrences (all)	1 / 88 (1.14%) 1	0 / 84 (0.00%) 0	
Injury, poisoning and procedural complications			
Intentional product misuse subjects affected / exposed occurrences (all)	0 / 88 (0.00%) 0	1 / 84 (1.19%) 1	
Medication error subjects affected / exposed occurrences (all)	2 / 88 (2.27%) 2	3 / 84 (3.57%) 3	
Overdose subjects affected / exposed occurrences (all)	1 / 88 (1.14%) 1	3 / 84 (3.57%) 3	
Vascular disorders			
Hypertension subjects affected / exposed occurrences (all)	1 / 88 (1.14%) 1	0 / 84 (0.00%) 0	
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	4 / 88 (4.55%) 4	0 / 84 (0.00%) 0	
Migraine subjects affected / exposed occurrences (all)	0 / 88 (0.00%) 0	1 / 84 (1.19%) 1	
Somnolence subjects affected / exposed occurrences (all)	1 / 88 (1.14%) 1	2 / 84 (2.38%) 2	
Blood and lymphatic system disorders			
Iron deficiency anaemia subjects affected / exposed occurrences (all)	1 / 88 (1.14%) 1	0 / 84 (0.00%) 0	
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 88 (1.14%) 1	0 / 84 (0.00%) 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	0 / 88 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	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 n° 7 of 11/Mar/2022 ) was made after first patient enrolled in the study. 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. The description of the "PGIC scale" was aligned with the validated one effectively submitted for the study.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported