Name of Sponsor/Company: Angelini Pharma S.p.A.	(For National Authority Use Only)
Name of the finished product: Not Applicable	
Name of the active substance: 380mg methocarbamol/300mg paracetamol Fixed-Dose Combination	

Study Title

Efficacy and safety of different dosage regimens of the combination methocarbamol/paracetamol in acute Low Back Pain (LBP): MioPain study

Study centres and Investigators

33 centres; 33 General Practitioners:

- 20 centres actively enrolled patients;
- 13 centres did not recruit any patients.

Publication (reference) Not applicable

Study period (years)	**Study Phase**
First patient in: 07Oct2021. Last patient out 03Nov2023.	IV

Objectives

The aim of the present study was to assess the efficacy and safety of different dosage regimens of the combination methocarbamol/paracetamol in the treatment of patients with acute non-specific LBP.

The primary objective of the study was to assess the time to reach the complete relief from LBP, defined as a VAS score ≤ 5 mm at two consecutive assessments, starting from Day 1 up to Day7 (±1).

Secondary objectives were:

- assessments of degree of improvement of the intensity of LBP from Visit 0 to Visit 1;
- improvement of the intensity of LBP from Visit 0 to Final Visit;
- improvement in the mobility restriction from Visit 0 to 1 and Final Visit;
- improvement in the functional disability from Visit 0 to 1 and Final Visit;
- assessment of the patients' global impression at Visit 1 and Final Visit;
- assessment of the clinical global impression - improvement at Visit 1 and Final Visit;
- safety assessment.

Methodology

This is a Phase IV, randomized, open-label, parallel-group, multicentre study. Patients were randomized to one of the following 2 treatment groups:

- Group 1: methocarbamol 380 mg/paracetamol 300 mg (2 oral tablets 4 times/day)
- Group 2: methocarbamol 380 mg/paracetamol 300 mg (2 oral tablets 6 times/day)

The expected duration of patient participation into the trial (from ICF signature up to any applicable follow up) was 8 days (± 1). Patients' enrolment was competitive among clinical sites.

Number of subjects (planned and analysed)

A total of 192 patients of both sexes were calculated to be enrolled in the study and randomized 1:1 in the study groups.

Diagnosis and main criteria for inclusion

Inclusion criteria

1. Males and females of any ethnic origin between 18 and 64 years of age (limits included).
2. Patients with current episode of acute (pain lasting less than 6 weeks) non-specific LBP, defined as pain and discomfort, localised below the costal margin and above the inferior gluteal folds, with or without leg pain, or acute exacerbation of chronic low back pain defined with a VAS score ≥ 40 mm.
3. Patients with signs and symptoms of muscle spasm of the lumbar region, as clinically diagnosed by the Investigator.
4. Women of childbearing potential and women with no menses for a period < 12 months must have a negative pregnancy test at Visit 0 and adopt appropriate birth control method.
5. Patients legally capable of giving their consent to participate in the study and available to sign and date the written Informed Consent.

Exclusion criteria

1. 1. Known hypersensitivity or allergy to the active ingredients and/or to any component of the study medications.
2. Lactating and pregnant women.
3. Clinically significant abnormalities on physical examination and vital signs at Visit 0 which in the opinion of the Investigator could interfere with the study procedures or endpoints evaluation.
4. Suspicious (according to the patient's symptoms at baseline) or confirmed COVID-19 infection at time of screening visit.
5. History of cervical, thoracic, or lumbosacral pain for ≥75% of the time in the last year, or any other LBP episode in the last 3 months that required pharmacological treatment with an opioid analgesic.
6. Patients with:
    - serious spinal pathology; spinal surgery in the year prior to screening or history of more than one spinal surgery; history of severe lumbar spinal stenosis; ankylosing spondylitis; all cases of proven diagnosis of lumbosciatalgia including that caused by herniated disc; radiculopathy; severe arthritis and osteoporosis; muscular diseases, such as myositis, poliomyelitis, muscular dystrophy and myotonia; fibromyalgia; myasthenia grave; fracture or recent history of violent trauma of the back; serious structural deformity of the back;

- cancer, not in remission or in complete remission less than 1 year;
- active influenza or other viral syndrome; immunosuppression; systematically unwell; unexplained significant weight loss;
- women with the following conditions: polymenorrhea, endometriosis, ovarian cysts and uterine fibroids with a painful severe symptomatology that can lead to a wrong LBP diagnosis;
- widespread neurological symptoms (including cauda equina syndrome) or any brain disease; ever suffered from any brain damage or have been in a coma; epilepsy or seizures;
- active or suspected esophageal, gastric, pyloric channel, or duodenal ulceration, or bleeding in the last 30 days;
- previous treatment with anticoagulants in the seven days before the screening visit;
- renal and/or hepatic failure;
- acute hepatitis;
- cardiac or pulmonary diseases;
- acetylsalicylic acid-triggered asthma;
- glucose-6-phosphate dehydrogenase-deficient patients; glutathione deficiency, dehydration, chronic malnutrition; anemia.

Any other condition that, in the opinion of the Investigator, interferes with the study endpoints/procedures and does not justify the inclusion of the patient in the study.

7. Current use of full, regular, recommended doses of any skeletal muscle relaxants/non – opioid analgesics/anti-inflammatory/Non-steroidal anti-inflammatory drugs in the 6 hours prior to the screening visit. Use was forbidden for the entire trial duration.
8. Current use of full, regular, recommended doses of or any medication that can alter the perception of pain (e.g., opioids, heparinoids, psychotropic agents, anti-H1 agents or glucocorticosteroids, etc.), in the 24 hours prior to the screening visit. Use was forbidden for the entire trial duration.

   Chronic intake of low doses of acetylsalicylic acid, i.e., ≤162 mg/daily, taken for at least 30 days prior to the first dose of study medication for non-analgesic reasons could be continued for the duration of the study.
9. Current use of the following medications (use was forbidden for the entire trial duration):
   - systemic corticosteroids;
   - other drugs containing paracetamol;
   - central nervous system (CNS) depressants and stimulants, including barbiturates, anaesthetics, appetite suppressants, anticonvulsants and lamotrigine (with the exception of therapeutic doses of benzodiazepines used as hypnoinducers in patients stabilised for more than one month since the screening visit);
   - anticholinergic drugs; psychotropic drugs; anti-cholinesterase drugs, pyridostigmine;
   - oral anticoagulants;
   - chloramphenicol; rifampicin; zidovudine;
   - loop diuretics;
   - isoniazid; probenecid;
   - propranolol;
   - antiemetics;
   - metoclopramide; domperidone;
   - ion exchange resins (e.g. cholestyramine).
10. Patients undergoing physiotherapy, osteopathy or chiropractic treatments aimed to reduce LBP.
11. Patients treated with invasive procedures aimed to reduce LBP (e.g., epidural injections, spinal cord stimulation therapy).
12. History of alcoholic/substance abuse. Use of alcohol was forbidden during the entire duration of the study.
13. Inability to comply with the protocol requirements, instructions or study-related restrictions (i.e., uncooperative attitude, inability to return for study visits, unlikelihood of completing the clinical study); vulnerable patients (i.e., persons kept in detention).

14. Patients involved in the conduct of the study (i.e., Investigator or his/her deputy, first grade relatives, pharmacist, assistant or other personnel).
15. Participation to an interventional clinical trial within 3 months prior to Visit 0.

Test product, dose, mode of administration, batch number

At screening, patients were randomly allocated to one of the following two treatment groups:

Group 1: methocarbamol 380 mg/paracetamol 300 mg FDC, tablets. Two tablets 4 times daily up to 7 days (i.e., every 6 hours±1 hour).

Group 2: methocarbamol 380 mg/paracetamol 300 mg FDC, tablets. Two tablets 6 times daily up to 7 days (i.e., every 4 hours±1 hour).

All the patients, in both groups, were treated with tablets with the same batch number (# 3650, expiry date 28/Feb/2026) for the entire duration of the study.

Reference therapy, dose, mode of administration, batch number

Not applicable. This study had no control group.

Duration of treatment

The patient was instructed to stop taking the treatment if two consecutive LBP assessments were ≤ 5 mm on the VAS (home assessment). The maximum duration of the treatment was 7 (± 1) consecutive days.

Assessment criteria

Primary endpoint. Time when the complete pain relief was reached. A complete pain relief was defined as a VAS score ≤ 5 mm at two consecutive assessments starting from Day1 up to Day7 (±1).

Secondary endpoints. Change in LBP intensity from Visit 0 to Visit 1 and Final visit (V2), measured by VAS. Change in the degree hand-to-floor distance, at Visit 0, 1 and V2, measured by a cm graduated bar. Change in the Oswestry Disability Index score at Visits 0, 1 and V2. Patients' Global Impression of Change scale score at Visit 1 and V2. Clinical Global Impression-Improvement scale score at Visit 1 and V2,

Efficacy variables. Visual Analogue Scale (VAS), to assess intensity of LBP for primary and secondary endpoints. The following variables were used as secondary efficacy endpoints: Hand-to-floor distance; Oswestry Disability Index (ODI), Patients' Global Impression of Change (PGIC) scale and Clinical Global Impression-Improvement (CGI-I) scale.

Criteria of safety and tolerability. Safety was evaluated as secondary endpoint considering AEs monitoring and changes from baseline of systolic and diastolic blood pressure; hearth rate; body temperature, body weight and complete physical examination.

Statistical methods

Sample size. A sample size of 172 patients was calculated to provide 80% power to detect a difference between the Group 1 and Group 2 responder curves, at a two-sided alpha level of 0.05. Assuming a percentage of responders at Visit 2 of 60% in the Group 1 and of 80% in the Group 2 and considering a 10% drop out rate, 192 patients were considered needed to be enrolled.

Analysis sets. Screened Population (SCR): all patients who sign informed consent and personal data processing consent. Enrolled Population (ENR): all patients who sign informed consent, personal data processing consent and are not screening failure, irrespective of compliance with the study protocol. Safety Population (SP): all randomized patients who take at least one dose of the study medication. Modified Intention-to-Treat (m-ITT): all randomized patients who take at least one dose of the study medication and have at least two post-baseline LBP assessments. Per Protocol (PP) population: m-ITT population with no major protocol violations.

Analysis. Primary endpoint efficacy assessment was performed in the m-ITT and PP populations. The m-ITT population represented the primary analysis population to evaluate the primary efficacy endpoint. The Kaplan-Meier (KM) method was used to estimate the distribution of overall survivor function. Secondary endpoints were analysed by opportune descriptive statistics and statistical tests, depending on the nature of variables. Safety assessments were carried out on the SP including AEs and vital signs.

Summary

Efficacy results

Primary endpoint. Due to a recruitment that reached only slightly more than half the required number, it is not possible to draw statistically valid conclusions on the efficacy of the product in terms of time to complete relief of pain. Regarding the primary endpoint (complete pain relief defined as a VAS score ≤ 5 mm at two consecutive assessments starting from Day1 up to Day7) in this small sample of available patients, in the m-ITT population (n=90), the number of responders were 8 and 8 in group 1 and 2, respectively. It is not possible to determine the KM median. Sensitivity analyses performed to assess the impact of potential biases (i.e. from missing consecutive LBP assessments or premature study discontinuation) did not show significative variations from the results of the main analysis. Considering the PP population, 48 patients in Group 1 and 36 in Group 2, complete pain relief was achieved in 8 patients in Group 1 and 8 in Group 2. It was not possible to determine the KM median.

Secondary endpoints. Regarding the effects in the intensity of the LBP, 4 days after the first intake of IMP, in m-ITT population the reduction in pain intensity vs baseline was over 38%, in Group 1 and quite less (29%), in Group 2. Eight days after the first intake a further improvement vs baseline was observed and at the end of the study the final reduction was 55% in Group 1 and 51% n Group 2.

This study demonstrates that the treatment with the IMP is associated with an improvement in spinal mobility in acute LBP, measured by the Hand-To-Floor Distance. In fact, at the end of the study, in the m-ITT set, the improvement from baseline was approximately 9 cm in both groups. Considering that the mean baseline value was 26-27 cm in both groups, the clinical relevance of this change appears significant.

ODI is an index used worldwide by clinicians and researchers to quantify disability due to acute and chronic LBP and assess its effects on patient's quality of life. During the study, the score of this parameter improved by approximately one third in the first three days of treatment and by 50-60% at the end of the 7 days of treatment, in both cases. Considering the composition of the domains into which ODI is divided, the impact on quality of life associated with treatment with this IMP seems to be clear.

Finally, the patient's belief about the efficacy of treatment, measured through the PGIC scale, results in a noticeable improvement in around 75% of patients.

Comment. Although the primary endpoint of the study was not met, as mentioned above, an improvement in the clinical picture could be observed in the secondary endpoints, approximately of the same magnitude in the two groups, with regard to pain, spinal function and quality of life.

It should be noted that the comparison of results between groups is not statistically meaningful due to the fact that the original sample size was not reached so, no valid conclusions can be drawn.

Safety results

As regards safety, limited to a treatment duration that does not exceed 7 days, the treatment of LBP with a described FDC of methocarbamol and paracetamol allows the following conclusions to be drawn.

1. The ADR profile is that expected from these classes of products. The most frequent ones affect the gastrointestinal system or are symptoms such as asthenia, feeling cold, dizziness which in no case manifest themselves as serious or require specific treatments.
2. The absence of SADRs, the low number of patients with ADRs (12.9%), for which only in 11.1% the causal relationship is indicated as certain, the very low number of cases (2.2%) for which the doctor deemed it appropriate to suspend the treatment, indicate, taken together, a high degree of safety and ease of handling in the use of the product.
3. The available data suggest that a higher daily dosage may correspond to a greater incidence and severity of ADRs.
4. Regardless of the administration regimen, no signs emerge suggesting that the combination of methocarbamol and paracetamol could determine, on the short-term, effects on vital signs or physical findings.

Conclusion

This clinical trial was designed to evaluate the efficacy and safety of different dosage regimens of the combination methocarbamol/paracetamol in the management of patients with acute non-specific LBP condition.

Due to poor recruitment, consequence of the national emergency for the COVID-19 pandemic, and according to the investigators, the study was terminated two years after randomisation of the first patient. During this longer-than-expected recruitment period, only a little more than half of the planned patients had been recruited; the study had to be closed because it was not feasible to reach the estimated sample size.

Despite the limitations indicated above, the available data from this study showed that, as far as safety is concerned, the described oral FDC of methocarbamol and paracetamol is safe for a short-term treatment, even if it cannot be excluded a potential correlation between the incidence and severity of adverse reactions and higher daily doses of IMP.

Regarding the efficacy, as already mentioned, the insufficient sample size does not allow definitive conclusions to be drawn. However, despite this, the intensity of the LBP, the mobility of the spinal cord and, in general, quality of life, showed clinically significant improvement related to exposure to IMP.

Date of report

31Jan2025