SYNOPSIS

NAME OF SPONSOR Abiogen Pharma S.p.A.	**INDIVIDUAL STUDY TABLE** **REFERRING TO PART OF THE DOSSIER** Volume: Page:	**(FOR NATIONAL AUTHORITY USE ONLY)**
NAME OF FINISHED PRODUCT Intra-articular Clodronate		
NAME OF ACTIVE INGREDIENT Disodium Clodronate		
TITLE OF STUDY A randomised, double-blind, parallel-group, multicenter, placebo-controlled, dose-ranging study, to evaluate the efficacy and safety of clodronate ampoules at different dosages, after intra-articular administrations to patients affected by knee osteoarthritis		
PRINCIPAL INVESTIGATOR Prof. Maurizio Rossini		
STUDY CENTRE The study was conducted in 37 sites in 3 European countries: Italy (4), Czech Republic (8) and Poland (25).		
PUBLICATION (REFERENCE) Not published as of 22 February 2022.		
STUDY PERIOD Screening date of first patient in: 31-JUL-2020 Date of last patient completed: 01-JUL-2021	**PHASE OF DEVELOPMENT** Phase II	
OBJECTIVES Primary objective To assess the effects of different dosages of intra-articular disodium clodronate on the reduction in target knee pain, compared to placebo. Secondary objectives • To assess the effects of different dosages of intra-articular disodium clodronate on functional disability and rescue medication consumption; • To evaluate the safety and local tolerability of different dosages of disodium clodronate intra-articular injections.		
METHODOLOGY Randomised, double-blind, parallel group, multicenter, placebo-controlled study. The trial included five treatment arms and compared the efficacy and safety of clodronate administered in four different unit dose strengths (5, 10, 20, 30 mg disodium clodronate, all in 1 ml ampoules) with placebo (1 ml ampoules containing citrate buffer solution for injection).		
NUMBER OF PATIENTS (PLANNED AND ANALYSED) Analysed for safety: 276 Analysed for efficacy: 276 Planned: 660 Enrolled: 276 Completed: 243 (33 discontinued: due to adverse events (4), death (1), inclusion not met/exclusion criteria met (3), lack of efficacy (1), protocol violations (5), withdrawal of consent (9) and other reasons (10))		

MAIN CRITERIA FOR INCLUSION

Patients were enrolled at the screening visit (Visit 1), and after reviewing instrumental/laboratory tests performed during the screening period, if they met all the following criteria:

1. Male and female patients, aged 50–75 years;

2. Patients affected by knee osteoarthritis (OA), as defined by American College of Rheumatology (ACR) clinical and radiographic criteria for OA of the knee, and meeting the following conditions:

- Kellgren-Lawrence Grade 2 to 3 severity OA of the knee with presence of osteophytes determined from X-rays of the knee obtained within 6 months from the Screening visit; i.e. in the tibio-femoral compartment of the target knee with at least 1 osteophyte and measurable joint space, as diagnosed by standard X-rays (anterior- posterior view [weight bearing extension or semi-flexion] and lateral). In the case that a patient had not a valid X- ray within 6 months prior to Screening, the exam was performed during the screening period;
- Patients suffering from OA symptoms of the target knee for at least 6 months prior to the Screening visit. Note: patients with bilateral OA of the knee were allowed as long as they could differentiate pain in the target knee, did not need to use analgesics for treatment of their contralateral knee, and did not expect to receive treatment of the contralateral knee during the study. In the case that both knees were eligible for the study based on pain intensity, the knee with the greater Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Score at rest was selected as the target knee joint as long as the contralateral knee OA would not exclude the patient from the study and all other entry criteria were satisfied. If one knee was ineligible for the study, the eligible knee was selected as the target knee as long as the contralateral (ineligible) knee did not exclude the patient from the study and all other entry criteria were met;

3. Patients with spontaneous pain at the target knee of moderate to moderately severe intensity, defined as a score ≥40 mm and ≤ 80 mm at the screening visit in pain at rest, as measured by means of a 100 mm Visual Analogue Scale (VAS) in the WOMAC pain subscale. This was to be confirmed at the baseline visit (Visit 2);

4. Patients able to read and understand the language and content of the study material, understand the requirements for follow-up visits, willing to provide information at the scheduled evaluations and willing and able to comply with the study requirements;

5. Patients having discontinued use of all systemic analgesic/non-steroidal anti-inflammatory drugs (NSAIDs) therapy prior to the screening visit and agree not to resume them during study. Note: paracetamol was provided to patients as rescue medication;

6. If female of child-bearing potential, must have a negative urine pregnancy test at the screening visit and use a reliable form of contraception for a least 1 month prior to Screening and throughout the study. Note: to be considered females of non-child-bearing potential, females must be surgically sterile or postmenopausal as documented in medical history for at least 1 year. Highly effective birth control methods included: combined hormonal contraception (containing estrogens and progestogen) associated with inhibition of ovulation (oral, intravaginal, transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable); intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomised partner; sexual abstinence;

7. Patients having undergone the informed consent process and having signed an approved consent form.

Patients could not be enrolled at the screening visit (Visit 1), and after reviewing instrumental/laboratory tests performed during the screening period, if they met any of the following criteria:

1. Patients with body mass index (BMI) > 40 kg/m^2;

2. Patients with osteoarthritis secondary to other articular diseases;

3. Patients with history of septic arthritis in any joint;

4. Patients that are candidate for knee replacement within next 6 months;

5. Patients with clinically significant effusion of the target knee;

6. Patients with significant pain outside the target knee, including significant hip or back pain;

7. Patients with clinically significant valgus/varus deformities, ligamentous laxity, or meniscal instability as assessed by the Investigator;

8. Patients with any musculoskeletal condition affecting the target knee that would impair assessment of the effectiveness in the target knee (e.g. Paget's disease of bone);

9. Patients with presence of infections and/or skin diseases and/or skin wounds in the area of injection site;

10. Patients had arthroplasty at the target knee at any time;

NAME OF SPONSOR	**INDIVIDUAL STUDY TABLE**	**(FOR NATIONAL AUTHORITY USE ONLY)**
Abiogen Pharma S.p.A.	**REFERRING TO PART OF THE DOSSIER**	
NAME OF FINISHED PRODUCT	Volume:	
Intra-articular Clodronate	Page:	
NAME OF ACTIVE INGREDIENT		
Disodium Clodronate		

11. Patients having received viscosupplementation of the target knee or any other joint within 6 months before Screening;

12. Patients having received any topical prescription products (e.g., corticosteroids, NSAIDs, or capsaicin) for the target knee in the 2 weeks before Screening (Note: use of over-the- counter topical products such as antibiotics and 1% hydrocortisone were allowed for areas other than the target knee);

13. Patients having received systemic administration of steroidal anti-inflammatory drugs in the previous 8 weeks or systemic NSAIDs in the previous 7 days;

14. Patients having received paracetamol in the previous 12 hours;

15. Patients having received any intra-articular drug administration in the target knee in the previous 3 months (including any formulation of corticosteroids, or any investigational product);

16. Patients having received glucosamine, chondroitin-sulfate, diacerein and matrix metalloproteinase (MMP) inhibitors in the 4 weeks before Screening;

17. Patients having received parenteral or oral bisphosphonates in the 12 months before screening;

18. Patients having received denosumab in the 12 months before screening;

19. Patients having had any previous surgery in the target knee within 6 months prior to Screening, or any planned surgery throughout the duration of the study;

20. Patients having had diagnostic or surgical knee arthroscopy, or knee lavage in the target knee in the 6 months prior to Screening;

21. Patients with presence of serious gastrointestinal, renal, hepatic, pulmonary, cardiovascular, or neurological disease that could interfere with the outcome of the study or the patient's ability to comply with study requirements;

22. Patients with a current malignancy or had treatment for a malignancy, except non-melanoma skin cancer, within the past 5 years;

23. Patients with medical history of osteonecrosis of the jaw in the previous 24 months or at risk of osteonecrosis of the jaw;

24. Patients with history of kidney failure or renal insufficiency (creatinine > 2.0 mg/dl);

25. Patients with clinically significant abnormalities of laboratory parameters measured at the screening visit;

26. Known hypersensitivity to study drug or other bisphosphonates, including paracetamol (rescue medication);

27. Patients receiving treatments which could interfere with either the local application of study drug, or the evaluations of results;

28. Patients having received treatment with any other investigational product within 3 months of the screening visit;

29. Pregnant (positive urine test) or breastfeeding women, or planning to become pregnant during the study;

30. Patients with history of alcoholism or drug dependence;

31. Patients with inability to provide the informed consent.

INVESTIGATIONAL DRUG, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Active investigational medicinal product (IMP):

Clodronate: 1 ml ampoules containing unit dose strengths of 5, 10, 20, 30 mg disodium clodronate;

Dose regimen: one intra-articular injection, once monthly, for two consecutive months (two intra-articular injections in total).

Disodium clodronate for intra-articular administration in each of the four dose strengths and matched placebo was made available in indistinguishable ampoules.

Paracetamol tablets (rescue medication) was the only allowed pain relief medication during the study (up to the maximum daily dose of 3000 mg).

NAME OF SPONSOR	**INDIVIDUAL STUDY TABLE**	**(FOR NATIONAL AUTHORITY USE ONLY)**
Abiogen Pharma S.p.A.	**REFERRING TO PART OF THE DOSSIER**	
NAME OF FINISHED PRODUCT	Volume:	
Intra-articular Clodronate	Page:	
NAME OF ACTIVE INGREDIENT		
Disodium Clodronate		

Measurement of the efficacy parameters (WOMAC scale and pain on active movement of the target knee) was performed at a minimum of 6 hours from the last paracetamol administration. If administration of rescue paracetamol was required within 6 hours prior to the scheduled measurements, the WOMAC scale was assessed at home, using the eDiary, prior to the intake of the rescue paracetamol. In contrast, assessment of pain on active movement at a study visit was delayed until there was a minimum of 6 hours from the time of the last paracetamol administration.

Patients were instructed not to change dietary regimens and physical activity for the entire study duration.

In ascending order of patient number, patients qualifying for randomisation were assigned for treatment (in an equal proportion of patients in the five arms) in accordance with a pre- defined randomization scheme. A centralised randomisation procedure was used in the study

Used batch: Refer to Appendix A 5 Certificate of Analysis and Listing of Patients Receiving Investigational Drug(s) from Specific Batches

REFERENCE DRUG, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Reference treatment: Not applicable.

Placebo: 1 ml ampoules containing citrate buffer solution for injection.

Used batch: Refer to Appendix A 5 Certificate of Analysis and Listing of Patients Receiving Investigational Drug(s) from Specific Batches

DURATION OF TREATMENT

One month

CRITERIA FOR EVALUATION – SAFETY

The safety variables of the study were:

- General Treatment-Emergent Adverse Events (TEAEs);
- Local tolerability (pain, erythema, swelling and hardening in the site of IMP injection);
- Laboratory parameters: haematology (including ESR), clinical chemistry (ALT, AST, gamma-GT, hs-CRP, calcium, phosphate, sodium, potassium, alkaline phosphatase, albumin, creatinine) and urinalysis;
- Vital signs (heart rate, blood pressure, body weight);
- Physical examination;
- Global evaluation of tolerability by patient, measured by means of a 4-point rating scale.

CRITERIA FOR EVALUATION – EFFICACY

Primary efficacy variable

Change from baseline of WOMAC pain at rest in the target knee (0-100 mm VAS from item 4 of the WOMAC pain subscale), expressed as the best (i.e. the maximum decrease) of the pain intensity difference (PID) from baseline among measurements performed from Week 8 to Week 16, inclusive (i.e. the identified time frame in which the maximal effect can be expected).

Secondary efficacy variables

- Change from baseline of WOMAC pain at rest in the target knee (0-100 mm VAS from the WOMAC pain subscale) at each individual post-baseline time point;
- Change from baseline to Week 24 (end of study) or early discontinuation of WOMAC pain at rest in the non-target knee in patients with bilateral knee OA;
- Change from baseline of WOMAC total score, subscales (pain, stiffness and physical function) and single items (24 items), measured in the target knee using a 0-100 mm VAS) at each individual post-baseline time point;

NAME OF SPONSOR	**INDIVIDUAL STUDY TABLE**	**(FOR NATIONAL AUTHORITY USE ONLY)**
Abiogen Pharma S.p.A.	**REFERRING TO PART OF THE DOSSIER**	
NAME OF FINISHED PRODUCT	Volume:	
Intra-articular Clodronate	Page:	
NAME OF ACTIVE INGREDIENT		
Disodium Clodronate		

- Change from baseline of pain on active movement at the target knee, measured by means of a 100 mm VAS at each individual post-baseline visit;
- Patient assessment of Clinical Global Impression- Improvement (CGI-I) at each individual post-baseline visit;
- Change from baseline to Weeks 4, 8, 12, 16 and 24 in Short- form 36 (SF-36) total score, physical and mental components, single domains and single items;
- Use of rescue medication (paracetamol): number and proportions of users, and average pill count per day.

CRITERIA FOR EVALUATION – PHARMACOKINETICS

Not applicable.

STATISTICAL METHODS

Populations for Analysis

The study employed 5 analysis populations.

- Total Set

The Total Set consists of all subjects who provided informed consent on the 'Informed Consent' eCRF page.

- Screening Failures

Screening Failures are defined as subjects who provided informed consent but did not receive any Study Treatment (no date of First Study Treatment Administration on 'Study Drug Administration' eCRF page) and were not randomised to Study Treatment (no randomisation number recorded on the 'Randomisation' eCRF page). Screening Failures are summarised and presented by a Total count (without Study Treatment categorization).

- All Randomised Set

The All Randomised set contains all subjects who were Randomised ("Yes" entered in response to question "Has the patient been randomised?" on the 'Randomisation' eCRF page and a randomisation number assigned).

- Safety Analysis Set (SAF)

Safety Analysis Set (SAF) includes all patients who receive at least one dose of study treatment. SAF population is used for safety analyses. Patients are analysed belonging to the treatment group they were actually treated.

- Full Analysis Set (FAS)

Full Analysis Set (FAS). According to the intention-to-treat (ITT) principle, the FAS includes all Randomised patients who receive at least one dose of study treatment and having at least one post-baseline assessment of efficacy. The FAS population is used for all efficacy analyses. Patients are analysed as belonging to the treatment group they were Randomised to.

Primary and Secondary Efficacy Variables Analyses

Primary efficacy endpoint:

Primary efficacy was evaluated by the change from baseline in WOMAC pain at rest in the target knee (maximum decrease of pain among measurements performed from Week 8 to Week 16, inclusive). The treatment groups were compared using an analysis of covariance (ANCOVA) model that included treatment group as factor, and baseline value and country as covariates. For hypothesis testing, a hierarchical procedure was followed for this comparison that kept the overall level of statistical significance at 5% two-sided.

Firstly, the difference between the highest dose group (30 mg) and placebo was compared at the two-sided 5% level of significance. If this resulted in a significant result ($p<0.05$), the difference between the second highest dose group (20 mg) and placebo was compared at the two-sided 5% level of significance, otherwise no further statistical testing was performed and it was concluded to no significant differences between the dose groups and placebo.

NAME OF SPONSOR	INDIVIDUAL STUDY TABLE	(FOR NATIONAL AUTHORITY USE ONLY)
Abiogen Pharma S.p.A.	REFERRING TO PART OF THE DOSSIER	
NAME OF FINISHED PRODUCT	Volume:	
Intra-articular Clodronate	Page:	
NAME OF ACTIVE INGREDIENT		
Disodium Clodronate		

If the second highest dose group was significantly different from placebo, the third dose group (10 mg) was compared to placebo at the two-sided 5% level of significance, otherwise no further testing was performed and it was concluded to no significant difference between the three lower dose groups and placebo.

This approach was continued for the lower dose groups.

The last observation carried forward (LOCF) approach was to be used to deal with missing data or in the case of early study discontinuations. However, as the primary endpoint considered data over a time window (Week 8 to Week 16) and secondary endpoints were by visit, no imputation of missing data took place.

Secondary efficacy endpoints:

For secondary efficacy variables the same statistical methods described for the primary efficacy variable were used, but without using the hierarchical procedure.

Safety Variables Analyses:

All safety analyses were performed on the SAF. For each treatment group, Adverse Events (AEs) were summarized overall, by seriousness and by relationship to treatment. All other Safety variables were summarized by basic descriptive statistics or listed only.

Interim analysis

An interim analysis was performed after the randomisation of at least 250 patients. Only patients who were evaluable for primary efficacy endpoint were included in the analysis. The interim analysis was based on the evaluation of the primary endpoint in the five treatment arms (without performing formal inferential statistics). It was planned that the study would proceed to the end in case the difference in VAS for WOMAC pain at rest between the most effective clodronate arm and the placebo arm was ≥ 4 mm (i.e. half of the estimated minimum difference to demonstrate superiority). In the event that the difference in VAS for WOMAC pain at rest between the most effective clodronate arm and the placebo arm was < 4 mm, study interruption would be taken into consideration following the evaluation of the results in the placebo arm (i.e. following the estimation of the placebo effect).

Sample Size Calculation

Calculations were performed with NQuery 5.0. The hierarchical approach started with a comparison of the highest dose with placebo and for performing the sample size calculation this was defined as a single contrast in an analysis of variance (ANOVA), not taking covariates into account.

A sample size of 119 evaluable patients per treatment group would have 90% power, with a 0.05 two-sided significance level, to detect a difference between treatments of 8 mm in VAS for WOMAC pain at rest, assuming that the common standard deviation was 19 mm. The latter assumption was supported by internal data at Abiogen.

The stopping rule may lead to a small increase of the type 2 error and so the actual power may be a bit less than the one used in the above calculations. Quantifying this effect depended on the alternative hypothesis for the 5 group means and on the true common standard deviation and so would not lead to a single and exact answer. To be on the safe side, however a power of 90% instead of the often adopted 80% had been chosen.

Estimating a proportion of 10% of patients not evaluable for the primary efficacy endpoint, a total number of 660 patients (132 in each treatment group) were planned to be enrolled and randomised.

SAFETY RESULTS

Safety data was analysed for all 276 randomised patients. Out of the 276 patients, 237 Treatment Emergent Adverse Events (TEAEs) were reported in 115 patients (41.7%). 20 patients (7.2%) had 34 Adverse Drug Reactions (ADRs). The study drug related TEAEs by MedDRA PT were injection site pain (10 patients, 3.6%); joint swelling (2 patients, 0.7%); and administration site pain, injection site swelling, arthralgia, back pain, joint lock, myalgia, pain in extremity, contusion,

NAME OF SPONSOR	**INDIVIDUAL STUDY TABLE**	**(FOR NATIONAL AUTHORITY USE ONLY)**
Abiogen Pharma S.p.A.	**REFERRING TO PART OF THE DOSSIER**	
NAME OF FINISHED PRODUCT	Volume:	
Intra-articular Clodronate	Page:	
NAME OF ACTIVE INGREDIENT		
Disodium Clodronate		

ligament sprain, anaemia, gastrooesophageal reflux disease, C-reactive protein abnormal, red blood cell sedimentation rate increased, headache reported in 1 patient each. 10 patients (3.6%) experienced 16 serious adverse events (SAEs). The system organ classes of the SAEs were Infections and infestations (4 patients, 1.4%), Cardiac disorders and Injury, poisoning and procedural complications (each 2 patients, 0.7%), Gastrointestinal disorders, General disorders and administration site conditions, Nervous system disorders, and Respiratory, thoracic and mediastinal disorders (each 1 patient). The SAEs by MedDRA PT were Corona virus infection (4 patients, 1.4%) reported in 5mg Clodronate arm, 10mg Clodronate arm, 20mg Clodronate arm, and 30mg Clodronate arm; pneumonia (2 patients, 0.7%) reported in 10mg Clodronate arm and 30mg Clodronate arm; and myocardial infarction (placebo), myocardial ischaemia (10mg Clodronate arm), hand fracture (30mg Clodronate arm), jaw fracture (30mg Clodronate arm), medication error (30mg Clodronate arm), overdose (30mg Clodronate arm), small intestinal obstruction (5mg Clodronate arm), death (placebo), hemiparesis (5mg Clodronate arm), and dyspnoea (30mg Clodronate arm) reported in 1 patient each. One patient in the placebo arm had a TEAE with a fatal outcome. 3 patients (1.1%) discontinued due to 4 TEAEs of myocardial ischaemia, gastrointestinal viral infection, respiratory tract infection viral, ankle fracture. The system organ classes of the TEAE of the discontinued patients are Cardiac disorders, Infections and infestations and Injury, poisoning and procedural complications. The clinical laboratory evaluation showed no significant shifts from baseline. No Serious Adverse Reaction (SAR) occurred in this study. Overall, it can be concluded that the administration of intra-articular Clodronate was safe and well tolerated.

EFFICACY RESULTS

The primary efficacy variable of the study was the change from baseline of WOMAC pain at rest in the target knee (0-100 mm VAS from item 4 of the WOMAC pain subscale), expressed as the best (i.e. the maximum decrease) of the pain intensity difference (PID) from baseline among measurements performed from Week 8 to Week 16, inclusive (i.e. the identified time frame in which the maximal effect over placebo could be expected). The primary efficacy endpoint was tested using the null hypothesis that there was no difference between each dose group and placebo. From the primary efficacy analysis (p-value more than 0.05), it is not possible to reject the null hypothesis.

For the secondary efficacy analysis, the p-values for the change from baseline of WOMAC pain at rest in the target knee (0-100 mm VAS from the WOMAC pain subscale) at each individual post-baseline time point show at Week 5 that there were differences between the treatment groups: 20mg Clodronate vs Placebo, 10mg Clodronate vs Placebo and 5mg Clodronate vs Placebo.

The p-value of 0.552 for the change from baseline to Week 24 (end of study) or early discontinuation of WOMAC pain at rest in the non-target knee in patients with bilateral knee OA shows that there was no statistical significance.

The p-values for WOMAC Total Score at week 5 for the change from baseline of WOMAC total score, subscales (pain, stiffness and physical function) and single items (24 items), measured in the target knee using a 0-100 mm VAS) at each individual post-baseline time point show that there were differences between the treatment groups: 20mg Clodronate vs Placebo, 10mg Clodronate vs Placebo and 5mg Clodronate vs Placebo.

The p-values for WOMAC Pain subscale at week 4 and at week 5 for the change from baseline measured in the target knee using a 0-100 mm VAS) at each individual post-baseline time point show that there were differences between the treatment groups: 30mg Clodronate vs Placebo, 20mg Clodronate vs Placebo, 10mg Clodronate vs Placebo and 5mg Clodronate vs Placebo.

The p-values for WOMAC Stiffness subscale at week 5 for the change from baseline measured in the target knee using a 0-100 mm VAS) at each individual post-baseline time point show that there were differences between the treatment groups: 20mg Clodronate vs Placebo, 10mg Clodronate vs Placebo and 5mg Clodronate vs Placebo.

The p-values for WOMAC Physical functioning subscale at week 5 for the change from baseline measured in the target knee using a 0-100 mm VAS) at each individual post-baseline time point show that there were differences between the treatment groups: 20mg Clodronate vs Placebo, 10mg Clodronate vs Placebo and 5mg Clodronate vs Placebo.

The p-value of more than 0.05 at each visit for the change from baseline of pain on active movement at the target knee, measured by means of a 100 mm VAS at each individual post-baseline visit show that there was no statistical significance.

The p-value of more than 0.05 at each visit for the Patient assessment of Clinical Global Impression-Improvement (CGI-I) at each post- baseline visit show that there was no statistical significance.

NAME OF SPONSOR	**INDIVIDUAL STUDY TABLE**	**(FOR NATIONAL AUTHORITY USE ONLY)**
Abiogen Pharma S.p.A.	**REFERRING TO PART OF THE DOSSIER**	
NAME OF FINISHED PRODUCT	Volume:	
Intra-articular Clodronate	Page:	
NAME OF ACTIVE INGREDIENT		
Disodium Clodronate		

For the Physical components for the change from baseline to Weeks 4, 8, 12, 16 and 24 in Short-form 36 (SF-36) total score, the p-value of more than 0.05 at each visit show that there was no statistical significance. For the Mental components at week 12, the p-value indicates a difference only between 5mg Clodronate vs Placebo. For the Mental components at week 16, the p-value indicates a difference only between 30 mg Clodronate vs Placebo. For the Mental components at week 24, the p-value indicates a difference only between 30 mg Clodronate vs Placebo.

The p-values of more than 0.05 at each visit for the use of rescue medication (paracetamol) show that there was no statistical significance for average pill count per day. The descriptive analysis of the number and proportions of users at each visit suggests that there were no differences between the treatment groups.

For the secondary efficacy analysis, for some of the variables, a significant difference could be seen between the treatment groups while for other variables, there were no statistical significance. It can be generally concluded that there was no difference between each dose group and placebo.

PHARMACOKINETIC RESULTS

Not applicable.

CONCLUSIONS

The study was early terminated for evidence of futility of the Interim Analysis, as recommended by the Data Review Committee (DRC) report.

The primary objective was to assess the effects of different dosages of intra-articular disodium clodronate on the reduction in target knee pain, compared to placebo and the primary efficacy variable of the study was the change from baseline of WOMAC pain at rest in the target knee (0-100 mm VAS from item 4 of the WOMAC pain subscale), expressed as the best (i.e. the maximum decrease) of the pain intensity difference (PID) from baseline among measurements performed from Week 8 to Week 16, inclusive (i.e. the identified time frame in which the maximal effect over placebo could be expected). The primary efficacy endpoint was tested using the null hypothesis that there was no difference between each dose group and placebo. From the primary efficacy analysis (p-value more than 0.05), it is not possible to reject the null hypothesis.

The secondary objectives were to assess the effects of different dosages of intra-articular disodium clodronate on functional disability and rescue medication consumption and to evaluate the safety and local tolerability of different dosages of disodium clodronate intra-articular injections. The secondary efficacy variables were the change from baseline of WOMAC pain at rest in the target knee (0-100 mm VAS from the WOMAC pain subscale) at each individual post-baseline time point; the change from baseline to Week 24 (end of study) or early discontinuation of WOMAC pain at rest in the non-target knee in patients with bilateral knee OA; the change from baseline of WOMAC total score, subscales (pain, stiffness and physical function) and single items (24 items), measured in the target knee using a 0-100 mm VAS) at each individual post-baseline time point; the change from baseline of pain on active movement at the target knee, measured by means of a 100 mm VAS at each individual post-baseline visit; the patient assessment of Clinical Global Impression- Improvement (CGI-I) at each individual post-baseline visit; the change from baseline to Weeks 4, 8, 12, 16 and 24 in Short- form 36 (SF-36) total score, physical and mental components, single domains and single items; and the use of rescue medication (paracetamol): number and proportions of users, and average pill count per day. For the secondary efficacy analysis, for some of the variables, a significant difference could be seen between the treatment groups while for other variables, there were no statistical significance. It can be generally concluded that there was no difference between each dose group and placebo.

The safety variables of the study were general Treatment-Emergent Adverse Events (TEAEs); Local tolerability (pain, erythema, swelling and hardening in the site of IMP injection); Laboratory parameters: haematology (including ESR), clinical chemistry (ALT, AST, gamma-GT, hs-CRP, calcium, phosphate, sodium, potassium, alkaline phosphatase, albumin, creatinine) and urinalysis; Vital signs (heart rate, blood pressure, body weight); Physical examination; and Global evaluation of tolerability by patient, measured by means of a 4-point rating scale. Safety data was analysed for all 276 randomised patients. Out of the 276 patients, 237 Treatment Emergent Adverse Events (TEAEs) were reported in 115 patients (41.7%). 20 patients (7.2%) had 34 Adverse Drug Reactions (ADRs). The study drug related TEAEs by MedDRA PT were injection site pain (10 patients, 3.6%); joint swelling (2 patients, 0.7%); and administration site pain, injection site swelling, arthralgia, back pain, joint lock, myalgia, pain in extremity, contusion, ligament sprain, anaemia, gastrooesophageal reflux disease, C-reactive protein abnormal, red blood cell sedimentation rate increased, headache reported in 1 patient each. 10 patients (3.6%) experienced 16 serious adverse events (SAEs). The system organ classes of the SAEs were Infections and infestations

NAME OF SPONSOR Abiogen Pharma S.p.A.	**INDIVIDUAL STUDY TABLE** **REFERRING TO PART OF THE DOSSIER** Volume: Page:	**(FOR NATIONAL AUTHORITY USE ONLY)**
NAME OF FINISHED PRODUCT Intra-articular Clodronate		
NAME OF ACTIVE INGREDIENT Disodium Clodronate		

(4 patients, 1.4%), Cardiac disorders and Injury, poisoning and procedural complications (each 2 patients, 0.7%), Gastrointestinal disorders, General disorders and administration site conditions, Nervous system disorders, and Respiratory, thoracic and mediastinal disorders (each 1 patient). The SAEs by MedDRA PT were Corona virus infection (4 patients, 1.4%) reported in 5mg Clodronate arm, 10mg Clodronate arm, 20mg Clodronate arm, and 30mg Clodronate arm; pneumonia (2 patients, 0.7%) reported in 10mg Clodronate arm and 30mg Clodronate arm; and myocardial infarction (placebo), myocardial ischaemia (10mg Clodronate arm), hand fracture (30mg Clodronate arm), jaw fracture (30mg Clodronate arm), medication error (30mg Clodronate arm), overdose (30mg Clodronate arm), small intestinal obstruction (5mg Clodronate arm), death (placebo), hemiparesis (5mg Clodronate arm), and dyspnoea (30mg Clodronate arm) reported in 1 patient each. One patient in the placebo arm had a TEAE with a fatal outcome. No Serious Adverse Reaction (SAR) occurred in this study.

Three patients (1.1%) discontinued due to 4 TEAEs of myocardial ischaemia, gastrointestinal viral infection, respiratory tract infection viral, ankle fracture. The system organ classes of the TEAE of the discontinued patients are Cardiac disorders, Infections and infestations and Injury, poisoning and procedural complications. The clinical laboratory evaluation showed no significant shifts from baseline. Overall, it can be concluded that the administration of intra-articular Clodronate was safe and well tolerated.

In summary, the results of this final analysis, confirmed the safety profile of intra-articular Clodronate but its efficacy at the right dosage is yet to be proven.

VERSION IDENTIFICATION

Version 1.0, 22 February 2022