2. SYNOPSIS

<table>
<tr><td>Name of Company:
Chiesi Farmaceutici S.p.A.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(for National Authority Use only)</td></tr>
<tr><td>Name of Finished Product:
Clody®</td></tr>
<tr><td>Name of Active Ingredient:
Disodium clodronate 200 mg/4 ml solution with 1% lidocaine;
disodium clodronate 100 mg/3.3 ml solution with 1% lidocaine</td></tr>
<tr><td colspan="3">Title of Study: Multicentre, randomized, open-label, two-arm parallel groups, active controlled study design to demonstrate efficacy and tolerability of clodronate 200 mg/4 ml solution for intramuscular use with 1% lidocaine every other week vs. clodronate 100 mg/3.3 ml solution for intramuscular use with 1% lidocaine once-week in a 1-year treatment period of women with postmenopausal osteoporosis</td></tr>
<tr><td colspan="3">Investigators: 21 Principal Investigators in 3 countries</td></tr>
<tr><td colspan="3">Study Centre(s): The study was conducted in 21 centres in 3 countries (Italy, Bulgaria and Poland).</td></tr>
<tr><td colspan="3">Publication (reference): None</td></tr>
<tr><td colspan="2">Studied Period:
FPFV: 22 Nov 2011; LPLV: 04 Mar 2013</td><td>Phase of development: IIIb</td></tr>
<tr><td colspan="3">Objectives:
Primary:
The primary objective of the study was to demonstrate that disodium clodronate 200 mg/4 ml solution for i.m. use with 1% lidocaine administered every other week was not-inferior to disodium clodronate 100 mg/3.3 ml solution for i.m. use with 1% lidocaine administered once-a-week in terms of lumbar Bone Mineral Density (BMD) evaluated after 1 year (48 weeks) of treatment in women with postmenopausal osteoporosis.
Secondary: The secondary objectives of the study were:
• To assess the efficacy of the two investigational study drugs on lumbar BMD after 24 weeks of treatment;
• To assess the efficacy of the two investigational study drugs on femoral-neck BMD after 24 and 48 weeks of treatment;
• To assess the efficacy of the two investigational study drugs on biochemical markers of bone turnover at the screening visit, and after 24 and 48 weeks of treatment;
• To assess local pain and tolerability at the randomization visit and at the end of treatment;
• To assess the treatment compliance at each visit after randomization;
• To assess the safety of the two investigational study drugs as regards of frequency of adverse events, laboratory parameters and vital signs (heart rate and blood pressure).</td></tr>
<tr><td colspan="3">Methodology (Study Design):
This was a phase III, multinational, multicentre, open-label, randomised, two-arm parallel groups, active drug controlled study design.
Baseline BMD and biochemical markers of bone turnover were assessed during the screening visit (V0). A randomization visit (V1) took place within 14 days from V0 to confirm the eligibility criteria. Subjects satisfying all the inclusion and exclusion criteria then entered the 1-year treatment period. Clinic visits took place after 12 (V2), 24 (V3), 36 (V4) e 48 (V5) weeks from the randomization visit, with an acceptable variation of a maximum of ± 5 days in respect of the scheduled dates of the visits.</td></tr>
</table>

Number of patients

	Clodronate 200 mg/4 ml (C200)	Clodronate 100 mg/3.3 ml (C100)
Randomised population	131	129
Safety population	131	129
ITT population	126	119
PP population	112	107

Diagnosis and main criteria for inclusion:

- Subject's written informed consent obtained prior to any study-related procedures;
- Postmenopausal (any menses in the last 5 years) female subjects ≥ 50 years old with lumbar T-score < -2.5 and > -4 or femoral-neck T-score < -2.5 and > -3;
- At least three intact vertebrae between L1 and L4 and two evaluable vertebrae for DXA;
- Patients treated according to the non-pharmacological standard of care;
- Patients with the possibility and willingness to take the i.m. injections.

Test product, dose and mode of administration, batch number:

Disodium clodronate 200 mg/4 ml with 1% lidocaine, one i.m. injection every other week plus vitamin D3 25.000 I.U., one administration once-a-month.

Batch numbers: [redacted].

Duration of treatment: 48 weeks

Reference therapy, dose and mode of administration, batch number:

Disodium clodronate 100 mg/3,3 ml with 1% lidocaine, one i.m. injection once-a-week plus vitamin D3 25.000 I.U., one administration once-a-month.

Batch numbers: [redacted].

Criteria for evaluation:

Efficacy:

Primary variable

The primary efficacy variable was the value of lumbar BMD (evaluated with DXA) after 1 year of treatment (48 weeks). DXA scans were evaluated by a centralised laboratory through blinded reading.

Secondary variables

The secondary efficacy variables of the study were:

- Lumbar BMD evaluated after 24 weeks of treatment;
- Femoral-neck BMD evaluated after 24 weeks and 48 weeks of treatment;
- Bone turnover markers: CTX and BALP evaluated before starting treatment (at screening visit) and after 24 and 48 weeks of treatment;
- Compliance evaluated at each visit after randomization.

Safety:

The safety variables of the study were:

- Local pain and tolerability assessment evaluated at the randomization visit and at the last visit after 48 weeks of treatment;
- Adverse events (AEs) and adverse drug reactions (ADRs) evaluated at each visit after the screening visit;
- Vital signs (heart rate and blood pressure), measured at the screening visit and at each visit after the randomization visit;
- Laboratory safety parameters (hemochrome, creatininemia, azotemia, transaminases) evaluated at the screening visit and after 24 and 48 weeks of treatment.

Statistical methods

The following populations were considered for data analysis: Intention-to-Treat (ITT) population, which included all randomised subjects who received at least one administration of the study medication and with at least one available post-baseline evaluation of efficacy; Per-protocol (PP) population, which included all subjects from the ITT population without any major protocol deviations; safety population, which included all randomized patients who took at least one dose of the study medication.

The efficacy variables were analysed in both the ITT and the PP population (main analysis). Analysis of safety variables was performed in the safety population.

Descriptive statistics were provided for each variable in summary tables by treatment group. Quantitative variables were summarized by using n (number of patients), mean, median, and standard deviation, minimum and maximum. Categorical variables were summarized by using frequency count and percent distribution.

Efficacy:

Lumbar BMD values (in terms of T-scores) were summarized using descriptive statistics and 95% CI for the percent change from baseline to weeks 24 and 48 was calculated (based on absolute values). The assessment of non-inferiority was evaluated by calculating the two-sided 95% CI for the difference between the test and the reference treatments in mean percent change from baseline to week 48 by using an ANCOVA model with treatment and centre as factor and baseline as covariate. The test treatment was to be declared as not inferior to the reference treatment if the lower limit of this interval was ≥ -1.5 percentage points. The same analysis was repeated using data measured by local laboratories. An ANCOVA model was also used in the comparison between groups at week 24.

Femoral neck BMD values (in terms of T-score) were summarized using descriptive statistics and 95% CI for the percent change from baseline to weeks 24 and 48 was calculated (based on absolute values). The comparison between groups after 24 and 48 weeks of treatment was performed by using two separate ANCOVA models with treatment and country as factor and baseline as covariate.

Serum level of turnover bone biomarkers (CTX and BALP) were summarized using descriptive statistics and 95% CI for the percent change from baseline to weeks 24 and 48 was calculated (based on absolute values). The comparison between groups on log-transformed values was performed by using an ANCOVA model for repeated measures with treatment, visit, interaction between treatment and visit and country as fixed effects and baseline as covariate. Treatment difference on the log scale was back-transformed to the original scale and the effect was quantified in terms of ratio between geometric means.

Safety:

Local pain assessment: VAS score was summarized using descriptive statistics at each time point (before administration, immediately and 30 minutes after injection). VAS score was compared between groups immediately after injection using an ANOVA model with treatment and country as factors.

Local tolerability assessment: reddening and hardening scores were summarized using descriptive statistics at each time point (immediately and at 30 minutes after injection). Reddening and hardening scores at 30 minutes after injection were compared between groups at each time point using the Cochran-Mantel-Haenszel test stratified by centre.

Adverse events: AEs were tabulated by System Organ Class (SOC) and Preferred Term (PT). The number of AEs, SAEs, severe AEs, ADRs and AEs leading to discontinuation from the study, and the number and the percentage of patients experiencing AEs, SAEs, severe AEs, ADRs and AEs leading to discontinuation from the study were summarized for each treatment group. The comparison between groups was performed by means of Chi-square test or Fisher's exact test.

Vital signs: heart rate and blood pressures were summarized using descriptive statistics. 95% CIs for the changes from baseline (Visit 0) were calculated at each visit after randomization

Laboratory parameters: shift tables from baseline to 24 and 48 weeks with regard to normal range were presented for each treatment group. Hemochrome, creatininemia, azotemia and transaminases were summarized using descriptive statistics, and 95% CIs for the changes from baseline were calculated after 24 and 48 weeks of treatment.

Study population:

A total of 260 patients were randomised to receive the assigned treatment: 131 were assigned to the C200 group and 129 were assigned to the C100 group). Overall, 35 patients discontinued the study, 16 (12.2% of randomised) in the C200 group and 19 (14.7%) in the C100 group. Withdrawal of consent was the most common reason for study discontinuation, with 10 patients (7.6%) in the C200 group and 14 (10.9%) in the C100 group.

Extent of exposure and compliance:

The mean (± SD) extent of exposure was 46.2 ± 8.1 weeks (median 48 weeks, range: 6-52 weeks) in the C200 group and 46.9 ± 5.5 weeks (median 48 weeks, range: 12-52 weeks) in the C100 group.

The mean (± SD) overall compliance to the study medications was 104.4 ± 9.6 % (median 104.2 %, range 44-133 %) in the C200 group and 102.2 ± 4.5 % (median 102.1 %, range 80-115 %) in the C100 group. The difference between groups was statistically significant (p = 0.020).

Summary – Conclusions:

Efficacy Results

Primary variable: (lumbar BMD after 1 year of treatment)

PP population

The mean lumbar BMD values increased from baseline to week 48 in both groups. The mean (SD) percent change from baseline to week 48 was 1.59 (4.09) in the C200 group and 2.03 (4.23) in the C100 group. The adjusted mean percent difference between the C200 group and the C100 group was -0.340 (95% CI -1.420 to 0.740, p = 0.535). The lower limit of the 95% CI of the adjusted mean percent difference between the C200 group and the C100 group was ≥ –1.5, thus indicating that C200 was not inferior to C100 in primary efficacy variable.

In the sensitivity analysis performed on the local laboratory data, the adjusted mean percent difference between the C200 group and the C100 group was -0.131 (95% CI -1.251 to 0.989, p = 0.818). The lower limit of the 95% CI of the adjusted mean percent difference between the C200 group and the C100 group was ≥ –1.5, thus confirming that C200 was not inferior to C100.

ITT population

The mean lumbar BMD values increased from baseline to week 48 in both groups. The mean (SD) percent change from baseline to week 48 was 1.45 (4.33) in the C200 group and 2.03 (4.23) in the C100 group. The adjusted mean percent difference between the C200 group and the C100 group was -0.489 (95% CI -1.603 to 0.624, p = 0.387). The lower limit of the 95% CI of the adjusted mean percent difference between the C200 group and the C100 group was slightly lower than –1.5, thus indicating that the pre-defined criterion of non-inferiority in primary efficacy variable was not fully satisfied.

In the sensitivity analysis performed on the local laboratory data, the adjusted mean percent difference between the C200 group and the C100 group was -0.284 (95% CI -1.428 to 0.860, p = 0.625). The lower limit of the 95% CI of the adjusted mean percent difference between the C200 group and the C100 group was ≥ –1.5, thus indicating that C200 was not inferior to C100.

Secondary variables:

Lumbar BMD at week 24

In the PP population, the mean BMD increased from baseline to week 24 in both groups. The mean (SD) percent change from baseline to week 24 was 2.13 (3.63) in the C200 group and 1.88 (3.56) in the C100 group. The adjusted mean percent difference between the C200 group and the C100 group was 0.340 (95% CI -0.607 to 1.287), thus showing that the difference between groups was not statistically significant (p = 0.480).

The results in the ITT population were consistent with those observed in the PP population.

Femoral neck BMD:

In the PP population, the mean (SD) percent change from baseline to week 48 was 0.07 (5.73) in the C200 group and 0.42 (3.86) in the C100 group. The adjusted mean percent difference between the C200 group and the C100 group at week 48 was -0.358 (95% CI -1.631 to 0.915), thus showing that the difference between groups was not statistically significant (p = 0.580), as well no significant differences between groups were observed at week 24 (p = 0.218).

The results in the ITT population were consistent with those observed in the PP population.

CTX:

The mean CTX decreased from baseline to both week 24 and week 48 in both groups. The mean (95% CI) geometric mean ratio from baseline to week 48 was 0.903 (0.819 to 0.995) in the C200 group and 0.906 (0.826 to 0.994) in the C100 group.

The adjusted geometric mean ratio between the C200 group and the C100 group at week 48 was 0.988 (95% CI 0.882 to 1.106), thus showing that the difference between groups was not statistically significant (p = 0.832), as well no significant differences between groups were observed at week 24 (p = 0.547).

The results in the ITT population were consistent with those observed in the PP population.

BALP:

The mean BALP decreased from baseline to both week 24 and week 48 in both groups.

The mean (95% CI) geometric mean ratio from baseline to week 48 was 0.852 (0.798 to 0.909) in the C200 group and 0.884 (0.839 to 0.931) in the C100 group. The adjusted geometric mean ratio between the C200 group and the C100 group was 0.965 (95% CI 0.897 to 1.037), thus showing that the difference between groups was not statistically significant (p = 0.325), as well no significant differences between groups were observed at week 24 (p = 0.743).

The results in the ITT population were consistent with those observed in the PP population.

Safety Results:

Adverse events:

AEs were reported in 46 patients (35.1%) in the C200 group and in 53 (41.1%) in the C100 group (p = 0.322 between groups). SAEs were reported in 2 patients (1.5%) in the C200 group and in 9 (7.0%) in the C100 group: the difference between groups was statistically significant (p = 0.029). None of SAEs was fatal or treatment-related. Treatment-related AEs were reported in 4 patients (3.1%) in the C200 group and in 10 (7.8%) in the C100 group (p = 0.093 between groups). AEs of severe intensity were reported in 3 patients (2.3%) in the C200 group and in 2 (1.6%) in the C100 group (p = 1.000 between groups). AEs leading to study discontinuation were reported in none of patients (0.0%) in the C200 group and in 4 patients (3.1%) in the C100 group (p = 0.059 between groups).

In the analysis of total AEs, infections and infestations, with 21 patients (16.0%) in the C200 group and 21 (16.3%) in the C100 group, and musculoskeletal and connective tissue disorders, with 14 patients (10.7%) in the C200 group and 11 (8.5%) in the C100 group, were the most commonly involved SOCs. The most commonly reported TEAEs by PT were: nasopharyngits, with 3 patients (2.3%) in the C200 group and 7 (5.4%) in the C100 group, pharyngitis, with 5 patients (3.8%) in the C200 group and 3 (2.3%) in the C100 group, and back pain, with 5 patients (3.8%) in the C200 group and 3 (2.3%) in the C100 group. Five and ten fracturative episodes were reported in 5 and 8 patients in the C200 group and in the C100 group, respectively. In both treatment groups, there were no adverse events due to alterations in renal function.

In the analysis of treatment-related AEs, general disorders and administration site conditions, with 3 patients (2.3%) in the C200 group and 4 (3.1%) in the C100 group, were the most commonly involved SOC. Local reactions in the site of injection were reported in comparable rates in the two groups.

TEAEs leading to study discontinuation in the C100 group consisted of atrial fibrillation, conjunctivitis, keratoconjunctivitis sicca, nausea, femoral neck fracture, arthralgia and hot flush (each in one patient). Only one TEAEs leading to study discontinuation (conjunctivitis) was considered as treatment-related.

Laboratory parameters:

In both groups, there were no substantial changes from baseline to week 48 for all haematology and biochemistry parameters. Most of patients in both groups had normal values of haematology and blood chemistry parameters at both baseline and week 48. In both groups, there were no changes from baseline in renal function parameters.

Vital signs:

In both groups, there were no substantial changes from baseline to week 48 for all vital signs parameters (heart rate and blood pressure).

Local tolerability:

Local pain assessment: VAS score

The mean VAS score measured before injection, immediately after injection and 30 minutes after injection was comparable in the two treatment groups at both baseline and week 48, The comparison between groups of VAS score measured immediately after injection at baseline (mean ± SD: 1.76 ± 2.43 in the C200 group and 1.75 ± 2.30 in the C100 group) and at week 48 (mean ± SD: 1.75 ± 2.35 and 1.33 ± 1.91, respectively in the two groups) did not show statistically significant differences between groups at both visits (p = 0.980 and p = 0.134, respectively).

Reddening and hardening in the site of injection

The results of reddening showed that the distribution of patients across the score categories was comparable in the two groups at both baseline and week 48. Most of patients in both groups had no redness at both baseline and week 48. In the comparison between groups of the proportions of patients in each score category measured immediately after injection, no statistically significant differences were observed at both baseline (p = 0.352) and week 48 (p = 0.308).

The results of hardening showed that the distribution of patients across the score categories was comparable in the two groups at both baseline and week 48. Most of patients in both groups had no hardening at both baseline and week 48. In the comparison between groups of the proportions of patients in each score category measured immediately after injection, no statistically significant differences were observed at both baseline (p = 0.636) and week 48 (p = 0.262).

Conclusions:

- The results of the primary variable lumbar BMD measured in the central laboratory at week 48 in the PP population (i.e. the primary population for analysis) showed that disodium clodronate 200 mg/4 ml solution (C200) for i.m. use with 1% lidocaine administered every other week was not-inferior to disodium clodronate 100 mg/3.3 ml solution (C100) for i.m. use with 1% lidocaine administered once-a-week. Thus, the primary objective of the study was satisfied. The same findings were observed in the sensitivity analysis performed on data measured in the local laboratory.
- The comparisons between groups in lumbar BMD variable at week 24 did not show any statistically significant difference in both the PP and the ITT population, as well as there were no significant differences between groups in changes from baseline.
- The results of femoral neck BMD measured at both week 24 and week 48 also did not show statistically significant differences between groups.
- Treatment with the two IMPs was associated with decreases from baseline in mean values of CTX and BALP, without statistically significant differences between groups in both the PP and the ITT population.
- The mean compliance was significantly higher in the C200 group than in the C100 group. However, a good level of compliance to study medication was observed in both treatment groups.
- Both treatment regimens were well tolerated in terms of adverse events and local tolerability (pain, reddening and hardening in the site of injections).

Date of the report: 9 December 2013