Treatment of symptomatic knee osteoarthritis with oral salmon calcitonin: results from two phase 3 trials

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SUMMARY

Purpose: To evaluate the structure-modifying and symptom efficacy, as well as safety and tolerability of oral salmon calcitonin (sCT) formulated with a 5-CNAC carrier (a molecule based on Eligen® technology), in osteoarthritis (OA) patients with moderate to severe knee pain and joint structural damage classified as Kellgren and Lawrence (KL)2–3.

Methods and design: This is the combined reporting of two randomized, double-blind, multi-center, placebo-controlled trials (CSMC021C2301 and CSMC021C2302), evaluating the efficacy and safety of oral sCT in patients with painful knee OA with structural manifestations, enrolling 1176 and 1030 patients, respectively. Study subjects were randomized (1:1) to oral sCT 0.8 mg twice daily or placebo (PBO) for 24 months. The primary efficacy objectives were to examine the treatment effect compared to placebo on change over 24 months in joint space width (JSW) in the signal knee measured by X-ray, and to examine the change in pain and function using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) questionnaire. Other study parameters included patient and physician global assessment, and biochemical markers of bone (CTX-I) and cartilage degradation (CTX-II).

Results: At the 24 month endpoint there was no statistically significant treatment effect on joint space narrowing (JSN) in any of the two studies. In CSMC021C2301 there was a treatment effect on WOMAC (sum of pain, function, stiffness, and total scores) as well as on the biomarkers of bone and joint metabolism, but due to the hierarchical testing procedure the treatment effect was not claimed statistically significant.

Conclusions: The present formulation of oral sCT did not provide reproducible clinical benefits in patients with symptomatic knee OA (NCT00486434, NCT00704847).

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Introduction

Osteoarthritis (OA) is the most common form of arthritis1,2 with 20 million individual affected in the US alone. OA is a painful, disabling disease affecting the synovial joints resulting in strongly reduced quality of life. Currently there is no structure modifying treatments approved for OA. The exact etiology of OA is still relatively unknown, but risk factors such as age3, obesity4–6, genetic predisposition4–7, joint mal-alignment5, acute joint injury3,9 and reduced sex hormone levels in relation to menopause2 are known to be involved. There is an urgent medical need for development of a structure modifying treatment for OA. Several different approaches have been undertaken including bisphosphonates, INos inhibitors which until know all have failed pivotal phase III studies, albeit strontium ranelate did demonstrate positive effect on some parameters. As OA is a becoming recognized as a multi-factorial disease of the whole joint involving the bone, cartilage and synovium compartments, one single magic bullet for this diverse patient population may be a futile task.
Calcitonin, a 32-amino-acid peptide, has demonstrated protective activity on both bone and cartilage in many different OA models as well as preliminary clinical settings. Available as an injection or nasal spray since the 1970s to treat osteoporosis, calcitonin inhibits bone resorption by binding and activating to the calcitonin receptor on osteoclasts. An uni-molecular enhancer of gastrointestinal peptide absorption is the first protein developed for oral administration and assessed in a phase III clinical trial. Several Phase I studies have been performed to obtain a suitable oral formulation with optimal dosing parameters. These investigations have included (1) time of day for dosing (morning or evening), (2) food intake, (3) water intake, (4) synthetic vs recombinant productions of the peptide and was recently reviewed and published.

In the present study, we assessed the efficacy and safety of oral calcitonin in symptomatic OA in two phase III clinical studies.

Materials and methods

Study description

The two studies (CSMC021C2301, NCT00486434) and (CSMC021C2302, NCT00704847) were double blinded, randomized, placebo-controlled and multi-center phase III clinical trials for the assessment of an oral formulation of 0.8 mg calcitonin (Novartis Pharma AG) twice daily or matching placebo for 24 month, 19 sites in 11 countries. Patients aged 51–80 years with painful OA of at least one knee, but who were otherwise in good general health were recruited into two independent international double-blind Phase III trial. Patients were not to consume food for 1 h before receiving study medication. After taking each tablet with a maximum of 50 ml of water, patients were to wait at least 30 min, without further liquid, before consuming breakfast or dinner.

To be included, patients had to meet the American College of Rheumatology (ACR) criteria for diagnosis of OA. Both knees were assessed during the study, but a signal knee was identified prior to randomization for assessment of the primary efficacy endpoint. The signal knee had to be painful on most days of the prior month. Intra-articular injection of corticosteroids or hyaluronic acid in the signal knee was prohibited during the study and 3 months prior to randomization.

Randomization was stratified by center and it was ensured that treatment assignment was unbiased and concealed from patients and investigator staff. At study entry a patient was allocated the lowest available number on the randomization list available for the given site. The randomization list was produced by Novartis Drug Supply Management using a validated system that automated the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization numbers were linked to medication numbers. The SMC021 tablets were supplied to the investigators at a dose strength of 0.8 mg packaged in a blinded fashion. Matching placebo tablets were supplied in identical packaging.

The trial was conducted in accordance with the Declaration of Helsinki. The protocol was approved by independent ethics committees or institutional review boards (IEC/IRB). All subjects or legal representatives gave their informed consent to take part. The enrollment date was defined as the date the subject signed the Informed Consent.

X-RAY of the knee

X-rays images of both knees were obtained to assess the KL grading and JSW. A signal knee was identified prior to randomization for the assessment of the primary efficacy endpoints. The protocol was not fluoroscopically assisted. It was mandatory to use the Syna-Flex™ device, to make sure that the positioning was consistent. The subject was positioned in the equipment in a weight bearing position, flexing the knees until having the thighs in touch with Syna-Flex™, while the toes were touching the equipment. In order to ensure a similar degree of positioning in all subjects, there was a fixed external rotation of both feet determined by the Syna-Flex™ equipment.

Pain and function assessments

The subjects were instructed to read each question carefully and mark an X on the line that best represented their answer. The study staff only answered technical questions that did not bias the subject’s ratings. Pain, stiffness and function were assessed by the Western Ontario and McMaster Universities Arthritis (WOMAC) questionnaire version VA3.128 and 24 h patient reported pain (visual analogue scales (VAS) pain) as well as patient/physician’s global assessment of disease activity, were assessed by VAS on a 100 mm VAS by placing an X on the line that best described the pain, where 0 equaled to “No Pain” and 100 equaled to “Worst Pain Imaginable, or “Very Good” to “Very Poor.” The WOMAC scale is designed to assess pain, stiffness and physical function in patients with knee OA. The three domains (i.e., pain, stiffness and physical function) are represented by 5, 2 and 17 questions, respectively. The version used in these studies were the 100 mm VAS giving each question a score from 0 to 100. The range for the pain domain is 0–500, the range for stiffness is 0–200 and the range for function is 0–1700.

The subjects were informed not to take any analgesics for 3 days prior to this test prior to all visits where these questionnaires were completed. Outside 3 days prior to a visit with questionnaires the patients were allowed concomitant analgesic usage of NSAIDs, Paracetamol and combinations thereof with low-dose codeine. This was recorded by the subjects on diaries that were transferred to the Electronic Care Report Forms.

Blood and urine sampling

Blood and urine samples for serum measurement of bone and cartilage biomarkers were taken at baseline and every 6 months and sent to a central laboratory for assessment. Plasma samples were forwarded to Novartis for assessing levels of sCT and calcitonin antibody (at 0 and 24 months). All blood samples were obtained after overnight fasting and by vein puncture before study drug administration. Second morning void urine samples were to be collected at the clinic.
Statistical analysis

Sample size estimation

Each of the studies was powered to demonstrate significance at the 5% level of significance (two-sided test) in the co-primary endpoints. For the JSN it was assumed a 0.17 mm decrease in JSW per year in the placebo group, a 40% protection of progression in the treatment group, and a common standard deviation of 0.5 mm. For the WOMAC pain score an improvement of 8 mm at the 2-year endpoint was assumed for the placebo group, improvement of 40 mm in the treatment group, and a common standard deviation of 120 mm. For the WOMAC function score an improvement of 60 mm at the 2-year endpoint was assumed for the placebo group, improvement of 160 mm in the treatment group, and a common standard deviation of 400 mm. Given the assumptions above and assuming a dropout rate of 30% the CSMC021C2301 was powered by 97% on JSW, 96% on WOMAC pain, and 94% on WOMAC by enrollment of 575 subjects per treatment group, and CSMC021C2302 was powered by 93% on JSW and 92% by enrollment of 460 subjects per treatment group.

Baseline characteristics

Student’s t test and Fishers exact test were used to compare baseline characteristics in demographic or other characteristics between the two studies.

Efficacy parameters

The primary analytical approach for CSMC021C2301 was to use inferential testing to demonstrate the benefit of oral sCT to maintain JSW and to reduce pain and functional disability measured by the WOMAC scores compared to placebo. A hierarchical testing procedure was implemented (1. JSW, 2. WOMAC pain, 3. WOMAC function) on a two-sided significance level of 5%. The two-sided P-values had to be in favor of sCT in order for the confirmatory testing procedure to continue. CSMC021C2302 included two co-primary endpoints of JSW and WOMAC pain tested in the same hierarchical order (1. JSW, 2. WOMAC pain). The statistical significance of the treatment effect was calculated from a mixed model with repeated measures and unstructured covariance matrix with baseline value as a covariate and body mass index (BMI) level at baseline, treatment, visit, baseline by visit interaction, BMI by visit

CONSORT DIAGRAM FOR 2301

Fig. 1. CONSORT diagrams.
interaction and treatment by visit interaction as factors (MMRM ANCOVA model). The effect size estimates of treatment difference (Active treatment - Placebo) incl 95% CIs were from the MMRM ANCOVA model. The MMRM ANCOVA model was the pre-specified primary analysis method with no imputation of missing data. The analysis of data of the combined studies was a post-hoc analysis not defined a priori and the combined data was analyzed in a MMRM ANCOVA model similar to the model of the individual studies.

In the MMRM ANCOVA model the data of the biomarkers relative to baseline were logarithmically transformed to obtain symmetry of variance.

All statistical analyses were performed using SAS© software, version 9.3.

Safety parameters

Analysis of Adverse Events (AEs) were focused on treatment emergent AEs in the safety population. The number and percentage of patients were summarized by treatment according to the primary system organ class and preferred term. Patients experiencing a specific AE more than once were categorized with the most severe AE reported.

Evaluation of laboratory determinations were focused on changes from baseline and presented in clinical shift tables (i.e., cross tabulations of low, normal, and high values from baseline to each treatment visit). Additionally frequency tables of clinical notable abnormal values were prepared.

Results

Consort description

The present study includes the analysis of two independent phase III clinical trials, CSMC021C2301 and CSMC021C2302, screening 1680 and 1568 subjects, respectively, where a total of 1176 and 1030 were randomized 1:1 to the two treatment arms [Fig. 1(A) and (B)]. The main cause of exclusion was failure to meet the inclusion criteria including a KL of the knee of more or less than
The number of completed were 394 and 300 in the treatment and 454 and 339 in the placebo group [Fig. 1(A) and (B)].

**Study demographics and baseline patient description**

The demographics of the intent-to-treat (ITT) population, which consisted of all patients randomized and received at least one dose of the study medication, are given in Table I, and the biomarker baseline values are given in Table II. Within each study the population was well balanced. Comparison of the two studies revealed statistically significant higher number of males in CSMC021C2302 (P = 0.0002), higher number of Asians (P < 0.0001), slightly higher JSW of target knee (P = 0.02), higher number of patients with KL grade 3 (P < 0.0001), more WOMAC pain (P = 0.002), and slightly higher levels of the biomarkers (serum CTXI: P = 0.003; serum OC: P = 0.0001; urine CTXI: P = 0.03; urine CTXII: P = 0.0004).

**Endpoint measures**

JSW was measured at baseline, 12 and 24 months. There was no significant treatment effect in either study of change in JSW at the 24 month study endpoint (target knee; P = 0.96; P = 0.25; non-target knee: P = 0.37; P = 0.8) (Fig. 2). The WOMAC questionnaire was completed at baseline, 3, 6, 12 and 24 months. Across the visits the WOMAC scores decreased in both studies irrespective of treatment. At the 24 month endpoint a treatment effect was observed in CSMC021C2301 with a larger decrease in WOMAC pain and function in signal knee in the treatment group than in the placebo group (P = 0.002, P = 0.008). The treatment effect is considered non-significant due to the hierarchical testing procedure. No treatment effect was observed in CSMC021C2302, in either WOMAC pain (P = 0.68) or WOMAC function (P = 0.97) (Fig. 3). The effect estimates of treatment difference at the various time points (Active treatment — Placebo) incl 95% CIs are given in Table IV.

**Biomarkers**

There was a 15–20% reduction in the bone resorption marker of serum CTXI in the sCT-treated group in the CSMC021C2301 study throughout the study period (Fig. 4, Table IV). Likewise initially there was a 20% reduction in CTX-I in the sCT-treated group in CSMC021C2302, which however declined to 8% at the 24 months study endpoint. There was a 12% reduction in bone formation marker of serum osteocalcin in the sCT-treated group in CSMC021C2301 throughout the study. In alignment with the bone resorption data, a similar decrease of 12% was found at month 12 in the sCT-treated group in CSMC021C2302, but this decrease was non persistent and at study end only a 2% decrease was observed. There was a 10% treatment decrease in the cartilage degradation marker of urinary CTX-II in CSMC021C2301 throughout the study period. In CSMC021C2302 a comparable treatment effect was observed in the first year of study, but the treatment effect diminished in the second year of the study. At the 24 months study end point a treatment effect was observed in CSMC021C2301 (urine CTX-I: P < 0.0001; serum OC: P = 0.0001; urine CTX-II: P = 0.0003), albeit no treatment effect in study CSMC021C2302 (urine CTX-I: P = 0.29; serum OC: P = 0.62; urine CTX-II: P = 0.57). The treatment effect is considered non-significant due to the hierarchical testing procedure.

**Table I**

Demographic characteristics in ITT population [n (%) and mean (SD)]

<table>
<thead>
<tr>
<th></th>
<th>2301</th>
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<td></td>
<td>sCT</td>
<td>Placebo</td>
<td>sCT</td>
<td>Placebo</td>
<td>sCT</td>
<td>Placebo</td>
</tr>
<tr>
<td>Sex – n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>169</td>
<td>(28.9)</td>
<td>201</td>
<td>(34.4)</td>
<td>199</td>
<td>(38.3)</td>
</tr>
<tr>
<td>Female</td>
<td>416</td>
<td>(71.1)</td>
<td>383</td>
<td>(65.6)</td>
<td>321</td>
<td>(61.7)</td>
</tr>
<tr>
<td>Sex – n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.6</td>
<td>(6.83)</td>
<td>64.4</td>
<td>(6.42)</td>
<td>64.4</td>
<td>(7.03)</td>
</tr>
<tr>
<td>Race – n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>532</td>
<td>(90.9)</td>
<td>532</td>
<td>(91.1)</td>
<td>442</td>
<td>(85.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>53</td>
<td>(9.1)</td>
<td>51</td>
<td>(8.7)</td>
<td>72</td>
<td>(13.8)</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>(0.1)</td>
<td>1</td>
<td>(0.1)</td>
<td>6</td>
<td>(1.2)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.1</td>
<td>(4.87)</td>
<td>28.8</td>
<td>(4.48)</td>
<td>29.1</td>
<td>(5.37)</td>
</tr>
<tr>
<td>JSW (mm)</td>
<td>3.35</td>
<td>(0.92)</td>
<td>3.39</td>
<td>(1.00)</td>
<td>3.42</td>
<td>(1.04)</td>
</tr>
<tr>
<td>KL index n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>513</td>
<td>(87.7)</td>
<td>513</td>
<td>(87.8)</td>
<td>406</td>
<td>(78.1)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>72</td>
<td>(12.3)</td>
<td>71</td>
<td>(12.2)</td>
<td>114</td>
<td>(21.9)</td>
</tr>
<tr>
<td>WOMAC pain (mm)*</td>
<td>237</td>
<td>(77)</td>
<td>238</td>
<td>(75)</td>
<td>244</td>
<td>(69)</td>
</tr>
<tr>
<td>WOMAC total (mm)*</td>
<td>1133</td>
<td>(373)</td>
<td>1137</td>
<td>(383)</td>
<td>1120</td>
<td>(383)</td>
</tr>
</tbody>
</table>

* Target knee.

**Table II**

Biomarker values at baseline in biomarker population (geometric mean and geometric ±1SD range)

<table>
<thead>
<tr>
<th></th>
<th>2301</th>
<th>2301</th>
<th>2302</th>
<th>2302</th>
<th>All</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sCT</td>
<td>Placebo</td>
<td>sCT</td>
<td>Placebo</td>
<td>sCT</td>
<td>Placebo</td>
</tr>
<tr>
<td>N</td>
<td>578</td>
<td></td>
<td>577</td>
<td></td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>584</td>
<td></td>
<td>580</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline serum CTXI (mg/ml)</td>
<td>0.220</td>
<td>(0.134–0.362)</td>
<td>0.216</td>
<td>(0.135–0.346)</td>
<td>0.237</td>
<td>(0.152–0.371)</td>
</tr>
<tr>
<td>Baseline serum OC (mg/ml)</td>
<td>22.6</td>
<td>(16.1–31.6)</td>
<td>22.4</td>
<td>(16.0–31.4)</td>
<td>20.0</td>
<td>(13.8–29.1)</td>
</tr>
<tr>
<td>Baseline urine CTXI (µg/mmol creatinine)</td>
<td>1.53</td>
<td>(0.84–2.77)</td>
<td>1.49</td>
<td>(0.84–2.65)</td>
<td>1.61</td>
<td>(0.94–2.74)</td>
</tr>
<tr>
<td>Baseline urine CTXII (ng/mmol creatinine)</td>
<td>236</td>
<td>(130–427)</td>
<td>223</td>
<td>(124–402)</td>
<td>264</td>
<td>(152–460)</td>
</tr>
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</table>
### Table III

CMSC021C2301 treatment emergent AEs

<table>
<thead>
<tr>
<th>AEs</th>
<th>sCT (n = 585)</th>
<th>Placebo (n = 584)</th>
<th>sCT (n = 520)</th>
<th>Placebo (n = 508)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one AE</td>
<td>548 (94%)</td>
<td>520 (89%)</td>
<td>474 (91%)</td>
<td>459 (90%)</td>
</tr>
<tr>
<td>AEs occurring with a frequency of ≥5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any musculoskeletal and connective tissue disorder</td>
<td>231 (39%)</td>
<td>267 (46%)</td>
<td>215 (41%)</td>
<td>232 (46%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>89 (15%)</td>
<td>93 (16%)</td>
<td>86 (17%)</td>
<td>111 (22%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>62 (11%)</td>
<td>59 (10%)</td>
<td>52 (10%)</td>
<td>54 (11%)</td>
</tr>
<tr>
<td>OA</td>
<td>36 (6%)</td>
<td>52 (9%)</td>
<td>14 (3%)</td>
<td>25 (5%)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>38 (6%)</td>
<td>30 (5%)</td>
<td>27 (5%)</td>
<td>23 (5%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>21 (4%)</td>
<td>30 (5%)</td>
<td>26 (5%)</td>
<td>20 (4%)</td>
</tr>
<tr>
<td>Any infections and infestations</td>
<td>231 (39%)</td>
<td>249 (43%)</td>
<td>197 (38%)</td>
<td>215 (42%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>43 (7%)</td>
<td>55 (9%)</td>
<td>34 (7%)</td>
<td>39 (8%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>36 (6%)</td>
<td>52 (9%)</td>
<td>46 (9%)</td>
<td>40 (8%)</td>
</tr>
<tr>
<td>Cystitis</td>
<td>35 (6%)</td>
<td>17 (3%)</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>28 (5%)</td>
<td>24 (4%)</td>
<td>20 (4%)</td>
<td>23 (5%)</td>
</tr>
<tr>
<td>Any gastrointestinal disorders</td>
<td>268 (46%)</td>
<td>150 (26%)</td>
<td>208 (40%)</td>
<td>152 (30%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>82 (14%)</td>
<td>18 (3%)</td>
<td>77 (15%)</td>
<td>15 (3%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>59 (10%)</td>
<td>26 (4%)</td>
<td>48 (9%)</td>
<td>21 (4%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>56 (10%)</td>
<td>25 (4%)</td>
<td>45 (9%)</td>
<td>27 (3%)</td>
</tr>
<tr>
<td>Any vascular disorders</td>
<td>160 (27%)</td>
<td>92 (16%)</td>
<td>128 (25%)</td>
<td>77 (15%)</td>
</tr>
<tr>
<td>Hot flush</td>
<td>104 (18%)</td>
<td>24 (4%)</td>
<td>88 (17%)</td>
<td>22 (3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>46 (8%)</td>
<td>52 (9%)</td>
<td>31 (6%)</td>
<td>39 (8%)</td>
</tr>
<tr>
<td>Any nervous system disorders</td>
<td>96 (16%)</td>
<td>87 (15%)</td>
<td>101 (19%)</td>
<td>73 (14%)</td>
</tr>
<tr>
<td>Headache</td>
<td>35 (6%)</td>
<td>28 (5%)</td>
<td>29 (6%)</td>
<td>27 (5%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>n.a.</td>
<td>n.a.</td>
<td>32 (6%)</td>
<td>17 (3%)</td>
</tr>
<tr>
<td>Any injury, poisoning and procedural complications</td>
<td>87 (15%)</td>
<td>95 (16%)</td>
<td>69 (13 %)</td>
<td>84 (17%)</td>
</tr>
<tr>
<td>Procedural pain</td>
<td>29 (5%)</td>
<td>20 (3%)</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Any metabolism and nutrition disorders</td>
<td>76 (13%)</td>
<td>64 (11%)</td>
<td>68 (13%)</td>
<td>66 (13%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>30 (5%)</td>
<td>36 (6%)</td>
<td>24 (5%)</td>
<td>24 (5%)</td>
</tr>
<tr>
<td>Any general disorders and administration site conditions</td>
<td>60 (10%)</td>
<td>53 (9%)</td>
<td>66 (13%)</td>
<td>46 (9%)</td>
</tr>
<tr>
<td>Any investigations</td>
<td>53 (9%)</td>
<td>53 (9%)</td>
<td>35 (7%)</td>
<td>32 (6%)</td>
</tr>
<tr>
<td>Any skin and subcutaneous tissue disorders</td>
<td>69 (12%)</td>
<td>36 (6%)</td>
<td>66 (13%)</td>
<td>42 (8%)</td>
</tr>
<tr>
<td>Any respiratory, thoracic and mediastinal disorders</td>
<td>48 (8%)</td>
<td>49 (8%)</td>
<td>43 (8%)</td>
<td>36 (7%)</td>
</tr>
<tr>
<td>Any cardiac disorders</td>
<td>38 (6%)</td>
<td>30 (5%)</td>
<td>30 (6%)</td>
<td>28 (6%)</td>
</tr>
<tr>
<td>Any surgical and medical procedures</td>
<td>27 (5%)</td>
<td>30 (5%)</td>
<td>20 (4%)</td>
<td>26 (5%)</td>
</tr>
</tbody>
</table>

**Fig. 2.** JSW change s) at 12 and 24 months (LS means ± 95% CIs MMRM ANCOVA model). Open circles: Placebo; Closed circles: 0.8 mg oral sCT. Number of subjects Pla/sCT: A) month 0: 584/585; month 12: 478/427; month 24: 454/394; B) month 0: 508/520; month 12: 407/377; month 24: 337/300; C) month 0: 1092/1105; month 12: 885/804; month 24: 791/694; D) month 0: 580/578; month 12: 473/420; month 24: 444/382; E) month 0: 503/515; month 12: 403/372; month 24: 330/295; F) month 0: 1083/1093; month 12: 876/792; month 24: 774/677.
The levels of sCT in plasma were assessed 15 min after dosing at the last visit at month 24. The levels are detailed in Fig. 5. These levels were significantly lower compared to previous studies with the oral formulation in phase I and II studies.

Safety measures

The safety population consisted of all patients treated that received at least one dose. There were markedly higher incidences of gastrointestinal disorders and hot flushes in the active treatment arms of both studies, but most markedly in the CSMC021C2301 study (Table III). No other AEs were markedly different between the two groups in either study.

Discussion

OA is leading cause of disability affecting the joint. The present investigation focused on symptomatic knee OA without further subtype identification and segregation—well knowing that an important discussion on sub phenotypes of OA is ongoing in the field[19]. This patient population may be representative to OA in general.
Presently two large phase III study in OA with a disease modifying drugs, has been undertaken and completed, the anti-resorptive bisphosphonate risiedronate\textsuperscript{30,31} and strontium ranelate\textsuperscript{32}, the first with a negative outcome, and the other with partial positive data. Other approaches have been investigated, and failed in phase II clinical settings either due to lack of efficacy or AEs, such as cathepsin K inhibitors, some MMP inhibitors\textsuperscript{33,34} and doxycycline\textsuperscript{35,36}. This highlights the notion that OA is a complicated disease, which affects multiple compartments in the joints, and targeting only one parameter may not provide the requested relief, neither for neither symptoms nor structure.

The present combined phase III clinical studies showed (1) No significant effect on JSN. (2) A potential effect on total WOMAC and WOMAC subscores was observed in one study although not claimed significant as the primary endpoint of JSN failed to show significance. (3) A potential small effect on markers of bone and cartilage degradation, CTX-I and CTX-II respectively, and no positive balance between bone formation and bone resorption.

JSN discussion

In neither of the present studies, a significant inhibition of JSN was achieved. The decrease in JSW in the placebo group at the 2-year endpoint was in alignment with the expected decrease of 0.34 mm used in the sample size calculations but the expected treatment effect of a 40% reduction corresponding to a treatment effect of 0.14 mm was not achieved. In CSMC021C2301 the treatment effect was 0.00 mm [95% CI: −0.09−0.08 mm], and in CSMC021C2302 the treatment effect was 0.06 mm [95% CI: −0.05−0.18 mm].

Pain function

At present there is a considerable debate in the literature on the effect of scT on pain, albeit no long term RCT have investigated these effects carefully\textsuperscript{37}. In the CSMC021C2301 study we observed an effect on pain, stiffness and function, but as a hierarchical testing procedure was applied for the co-primary endpoints no beneficial treatment effect can be claimed as the first endpoint of JSN failed to show significance. The treatment effect was not reproduced in the CSMC021C2302 study. Generally, a minimum reduction of 10% of the maximum possible total WOMAC score is accepted as clinically significant\textsuperscript{38}. The reduction observed in CSMC021C2301 in total WOMAC-score of 95 mm out of a total of 2400 mm, equals a reduction of 4%, which therefore does not qualify for clinical significance. In the context of drug tolerability vs level of pain reduction, it should be noted that significantly more patients discontinued the trial prematurely due to AEs in the group receiving active treatment compared to placebo. Emerging pain studies highlight that pain perception, and in particular OA referred pain, needs to be carefully investigated to understand the context of the pain mediation and possible effects\textsuperscript{39–42} suggesting that further patient segregation may be needed for understanding and optimal efficacy of scT on OA pain and pain subtypes.


**Biomarkers**

With regards to bone resorption, surprisingly, and in contrast to the 40% reduction in bone resorption seen in other studies\(^{16-18,22,43}\), we found only a 20% reduction in study CSMC021C2301 (the study with the significant effect on pain and function), and a transient effect in study CSMC021C2302. The biomarker population was considerably larger in CSMC021C2301 where all subjects were included whereas biomarkers were measured in a subpopulation of 149 subjects only in CSMC021C2302, which results in an imbalance. There was a 10% reduction in the bone formation marker of osteocalcin in the active group compared to placebo in CSMC021C2301. This is as expected for an anti-resorptive treatment, consequent to the coupling between bone resorption and bone formation. This has been observed for most traditional anti-resorptive treatments such as SERMS, estrogens, bisphosphonates, cathepsin K inhibitors and anti-RANKL\(^{44,45}\). There was 10% reduction in the cartilage degradation marker of urinary CTX-II in study CSMC021C2301, and a transient effect in study CSMC021C2302. This should be compared to the 25% decrease in CTX-II observed in previous studies of oral sCT\(^{16-18,22,43}\) of 24-h urine. Note the different between 24-h urine and spot measurement with up-to 65% decrease for CTX-I and 50% for CTX-II, in response to oral Calcitonin\(^{16,18,22-27}\). The 10% decrease in cartilage degradation may be insufficient to reach the threshold for detection by JSN. This discrepancy in biomarkers may result from the approximately four fold low exposure in the current study as seen in Fig. 5, as compared to previous studies\(^{18,23-27}\). Importantly, the present exposure levels of sCT were measured at the end point after 2 years, compared to earlier time points for the comparison studies. There may be compensatory mechanism hindering intestinal uptake for long term for sCT, albeit the phase II data did not suggest this trend\(^{43}\). Interestingly other anti-resorptives have shown a decrease in CTX-I (bone resorption) with no effect on cartilage degradation (CTX-II), suggestion that only selected interventions may have dual action potential\(^{46}\). The effect size of CTX-II needed to obtain a significant change in JSN or cartilage volume assessed by MRI, and a clinical significant benefit, remains to be identified. Many studies have demonstrated that high levels of CTX-II is associated with JSN\(^{47,48}\) and consequent hold prognostic value. While CTX-II has been suggested to be the best described and validated marker in the rheumatology field, the efficacy side of this marker needs a successful phase III study in OA to be validated, as with all other markers in the OA field\(^{49}\).
The safety profile was acceptable in both studies. Adverse reactions to calcitonin treatment were mainly gastrointestinal symptoms such as diarrhea, nausea and vomiting. These mild to moderate severe AEs disappear spontaneously when treatment is stopped. Recently FDA cautioned against the use of sCT in osteoporosis, due to a possible less favorable efficacy/safety ratio compared to other bone treatments. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM343748.pdf). There was no causality documented in calcitonin treatment, albeit caution was encouraged in assessing the risk-benefit ratio for various indications.

Safety

Conclusion

In conclusion, the present pivotal phase III clinical studies demonstrated no reproducible clinical effects on pain, and function of oral sCT. This in contrast to preclinical10 and clinical observations (phase 1 and 2)10,13,15,51. There is a direct linear relationship with exposure of calcitonin and effect on the biomarker CTX-I27, suggesting the lower levels of exposure to be one of the key parameters of the lack of efficacy, which need to be understood in larger details. Further studies and investigations are needed to understand the lack of effect on JSN, and the origin of this, and potentially to develop other molecules with higher potencies and more robust formulations.

Author contributions

MK, CC, ACBJ and BJR made the first draft of the manuscript. BJR, IB and CC made the protocols. PA performed parts of the study, and wrote sections of the manuscript. IB performed all statistical analysis. AB and JRA reviewed all data. All authors critically reviewed the last version of the manuscript and participated in the entire process.

Conflicts of interest

All authors but Peter Alexandersen are employees of Nordic Bioscience, a company engaged in biomarker research and development of treatments for OA. Peter Alexandersen is an employee of CCBR, a company engaged in biomarker research and development of treatments for OA. Novartis and Nordic Bioscience co-sponsored the studies.

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For the CSMC021C2301 study


For the CSMC021C2302 study

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Supplementary data

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