2 Synopsis

Name of finished product: Not applicable

Name of active ingredient: Salmon calcitonin (SMC021)

Study number: CSMC021C2302

EudraCT No. 2007-003016-60

Title of study: A randomized, double-blind, multi-center, placebo-controlled study to evaluate the efficacy and safety of oral salmon calcitonin in the treatment of subjects with knee osteoarthritis

Investigators: Peter Alexandersen et al

Study centers: The study was conducted at 18 centers in 10 countries: 6 centers in the US, 1 center in the UK, 1 center in Spain,1 center in the Czech Republic, 3 centers in Denmark, 1 center in Hong Kong, 2 centers in Poland, 1 center in Romania, 1 center in Belgium and 1 center in Canada.

Publication (reference): Not applicable

Study period

First patient first visit: 26 June 2008

Last patient completed: 6 April 2011

Phase of development: III

Objectives: The primary objective of the study was to examine the effect of SMC021 compared to placebo on 2 co-primary endpoints:

1. Joint space width (JSW) in the medial tibio-femoral knee joint in the signal knee measured by X-ray change from baseline over 24 months.
2. Pain subscore change from baseline over 24 months as assessed by the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index.

The secondary objectives of the study were to examine the following endpoints:

1. Function to be assessed by WOMAC function sub-score in the signal knee.
2. Stiffness and total WOMAC score in the signal knee.
3. Pain assessed by visual analogue scales (VAS) in the signal knee.
4. Physical activity assessed by VAS.

5. Patient's global assessment of disease activity (VAS).
6. Physician's global assessment of disease activity (VAS).
7. Disease progression in the signal knee evaluated by magnetic resonance imaging (MRI) (volume, area, thickness, curvature, smoothness, homogeneity).
8. Disease progression in the signal knee (other than percent change in JSW) evaluated by X-rays (including but not limited, to Kellgren-Lawrence index and osteophytosis).
9. Cartilage turnover reflected by the 24-hour urinary excretion of CTX-II.
10. Bone turnover reflected by the 24-hour urinary excretion of CTX-I.
11. Cartilage and bone turnover markers in frozen spot urine and fasting serum samples.
12. Evaluation of the non-signal knee for X-ray parameters and MRI parameters.
13. Correlations between JSW and changes in JSW, i.e. joint space narrowing (JSN), WOMAC scores, pain measures, MRI measures and biochemical markers.
14. Number of patients who did not respond to treatment, defined as >0.5 mm JSN in the medial compartment over 2 years.
15. Health-related quality of life as assessed by the EQ-5D.

The exploratory objectives were as follows:

- Investigation of new bone or cartilage markers that may become available.
- Evaluation of time to need for surgery in the signal knee (based on Investigator assessment)
- Evaluation of patient response to treatment in JSW analyzed by pain severity as classified by quartiles at baseline.
- Estimate pharmacokinetic (PK) parameters for the patient population, and explore relationships between PK and other parameters (e.g. demographics, safety, efficacy, concomitant medications).

The study was not completed as planned. In November 2010 all male subjects were terminated due to a potential prostate risk identified in an identical trial (CSMC021C2301) and all female subjects in the 12 months extension study were terminated due to the fact that the identical study CSMC021C2301 did not meet the JSW endpoint.

Methodology: This was a randomized, double-blind, placebo-controlled, multi-center, Phase III study in women and men with OA of the knee comparing treatment with 0.8 mg SMC021 orally twice daily to treatment with placebo over 24 months. At the baseline visit, patients whose eligibility was confirmed were randomized 1:1 to either 0.8 mg SMC021 twice daily or placebo twice daily. At least 25% of the randomized study subjects was to have a body mass index (BMI) equal to or above 30 kg/m2. Each patient was to participate in the treatment period for 24 months. The screening period was to occur within 56 days before randomization.

Number of patients (planned and analyzed): Planned: 920 patients, Randomized: 1030 patients (521 in the SMC021 group, 509 in the placebo group).
Completed study drug (24 months treatment): 639 patients (300 in the SMC021 group and 339 in the placebo group). Analyzed: the ITT and safety populations were identical with 1028 patients (520 in the SMC021 group and 508 in the placebo group).

Diagnosis and main criteria for inclusion
Enrollment targeted ambulatory women and men between 51 and 80 years of age suffering from painful knee OA. The patients were not to be receiving medication that affected cartilage or bone metabolism. They were to be free from any underlying condition, other than OA, that could result in abnormal cartilage and bone metabolism.

The signal knee was to fulfill:

- The criteria of the American College of Rheumatology (ACR): knee pain for most days of the prior month and at least 1 out of 3 of the following:

    1. Age over 50 years
    2. Morning stiffness of less than 30 minutes
    3. Knee crepitus (ACR criteria for OA of the knee)

- Kellgren-Lawrence Index: Grades II–III at the medial tibio-femoral joint (as defined in Appendix 16.1.1-Protocol-Appendix 2).
- The signal knee should fulfill American Rheumatism Association (ARA) criteria for classification: Functional class I, II or III (as defined in Appendix 16.1.1-Protocol-Appendix 3). A JSW ≥ 2.0 mm at medial tibio-femoral joint (measured on the X-ray)
- A WOMAC pain subscale (5 questions) should reach ≥ 150 mm..

Test product, dose and mode of administration, batch number: 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 packaging control numbers of the test drug and placebo are presented for each country and time period below.

Country	First 6 months	Second 6 months	Third 6 months	Fourth 6 months
Belgium	07-0503US	08-0432US	09-0191US	09-0514US
Canada	07-0503US	08-0558US	09-0191US	09-0514US
Czech Republic	08-0414US	09-0190US	09-0311US	09-0514US
Czech Republic	08-0605US	09-0190US	09-0311US	09-0514US
Denmark	07-0345US	08-0432US	09-0191US	09-0514US
Denmark	07-0503US	08-0432US	09-0191US	09-0514US
Denmark	07-0503US	08-0414US	09-0191US	09-0514US
Denmark	07-0503US	08-0558US	09-0191US	09-0514US
Hong Kong	07-0503 US	08-0414US	09-0191US	09-0514US
Hong Kong	07-0503US	08-0558US	09-0191US	09-0514US
Poland	07-0503US	08-0432US	09-0191US	09-0514US
Poland	07-0503US	08-0414US	09-0191US	09-0514US
Poland	07-0503US	08-0558US	09-0191US	09-0514US
Romania	07-0503US	08-0558US	09-0102US	09-0514US
Spain	07-0503US	08-0558US	09-0102US	09-0514US
Great Britain	07-0503US	08-0558US	09-0514US	09-0514US
United States	08-0558US	09-0102US	09-0514US	09-0714US

Batch numbers corresponding to packaging control numbers

Packaging control number	Placebo	SMC021
07-0503US	AEUS/2007-0216 AEUS/2007-0218	H380BD
07-0345US	AEUS/2007-2018	H380BD
08-0414US	AEUS/2007-0316	H488AE
08-0605US	AEUS/2008-0265	H440ID
08-0558US	AEUS/2007-0316	H539GE
08-0432US	H183HB	H488AE
09-0190US	AEUS/2008-0265	H539GE
09-0102US	AEUS/2008-0265	H617KE
09-0191US	AEUS/2007-0316	H617KE
09-0311US	AEUS/2008-0265	H539GE

Packaging control number	Placebo	SMC021
09-0514US	AEUS/2008-0265	H601AF
09-0714US	AEUS/2008-0265	H617KE
10-0161US	AEUS/2009-0023	H541GE
10-0174US	AEUS/2008-0265	H702IF

Duration of treatment: 24 months except for early terminated male subjects.

Reference therapy, dose and mode of administration, batch number: Placebo tablets matching the SMC021 tablets were supplied in packaging identical to that of the SMC021 tablets. For placebo batch and packaging control numbers, see above.

Criteria for evaluation

Efficacy: The two co-primary efficacy variables were absolute change from baseline to Month 24 in joint space width (JSW), and the pain subscore of the Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire.

Secondary efficacy variables were:

- WOMAC function sub-score.
- Stiffness WOMAC sub-score and and total WOMAC score.
- Pain assessed by visual analogue scales (VAS).
- Physical activity assessed by VAS.
- Patient's global assessment of disease activity (VAS).
- Physician's global assessment of disease activity (VAS).
- Magnetic resonance imaging (MRI).
- Knee X-rays
- Urinary excretion of CTX-II.
- Serum and urinary excretion of CTX-I.
- EQ-5D

Safety: Safety assessments consisted of collecting all AEs, including serious adverse events (SAEs), with their severity and relationship to study drug. They included the regular monitoring of hematology, blood chemistry, urinalysis (renal assessments), calcitonin antibodies, and regular assessments of vital signs, physical condition, and electrocardiograms (ECGs).

Bioanalytics: Plasma calcitonin concentrations were measured at Month 1 in a subset of patients participating in a population PK (Pop PK) sub-study and at Month 24 at sites in Denmark (introduced by Protocol-Amendment 4) but will be reported separately in the SMC021 Phase III PK Modeling Report

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The central laboratory analyzed serum CTX-I (S-Crosslaps, Elecsys) and osteocalcin as well as urine CTX I/creatinine and CTX-II/creatinine. It was originally planned that serum CTX-II be measured, but this was not done.

The specialized laboratory at Novartis analyzed blood samples taken at month 1 (Pop PK study) and at month 24 (or ET) to measure plasma calcitonin concentration, estimate PK parameters and evaluate relationships between PK and other parameters (e.g. safety, efficacy).

Statistical methods: The two co-primary efficacy variables (absolute change from baseline to Month 24 in JSW and WOMAC pain) were compared between treatment groups using a repeated measures analysis of covariance (ANCOVA) model, including the baseline BMI level and the baseline JSW or pain measurements, respectively, as covariates. The primary analysis, using a repeated measures ANCOVA model, was performed on the ITT population using hierarchical testing of the a priori ordered hypotheses (1. JSW, 2. WOMAC pain) on a significance level of 0.05 (two-sided). Two-sided p-values had to be in favor of SMC021 in order for the confirmatory testing procedure to continue.

Supportive analyses were performed with alternate methods for imputation of missing values, with additional baseline covariates, for the per-protocol population, for percent change (as opposed to absolute change), and (for JSW) as descriptive analyses according to the quartiles from the WOMAC pain subscale at baseline.

For all secondary efficacy parameters, change from baseline to Month 24 in the ITT population were analyzed using either standard ANCOVA or repeated measures with baseline value and BMI class as covariates.

Biochemical markers of cartilage and bone turnover were tabulated with summary statistics (including geometric mean) and, additionally, with the ratio to baseline.

In addition to standard summary statistics for safety analyses, analysis of pre-defined identified/potential risk AEs (using either standard MedDRA query terms or a group of pre-defined preferred terms, or a combination of both) were summarized by treatment group and separately for sex and age subgroups, including 95% CIs (Clopper-Pearson type) for the proportions. In addition, risk ratio and risk difference were calculated with 95% confidence intervals for SMC021 with placebo as reference.

Summary - Conclusions

Demographic and background characteristics: Overall, both treatment groups were well balanced with respect to demographic and disease characteristics The mean age of the population was 64 years, and approximately 85% of the population was White. About 61% of the patients were female, slightly less in the placebo group than in the SMC021 group. About 37% of the patients were obese (BMI $\geq$30 kg/m^2). About 79% of the patients had Kellgren-Lawrence Index grade II; about 65% had ARA classification functional class II.

Efficacy results: This study failed to demonstrate a treatment effect on the two co-primary endpoints. For JSN at month 24, mean (SD) absolute changes were −0.348 (0.7222) mm in the SMC021 group and −0.400 (0.7235) mm in the placebo group with between-treatment difference p=0.2620.

Similarly, there were no improvements in the WOMAC pain subscore and the WOMAC physical function subscore observed at month 24. For WOMAC pain, mean (SD) absolute changes were −98.4 (110.98) in the SMC021 group and −104.4 (109.29) in the placebo group, between-treatment p=0.6428. For WOMAC function, mean (SD) absolute changes were −281.1 (343.69) in the SMC021 group and −288.4 (374.56) in the placebo group, between-treatment p=0.8481. No statistically significant differences were seen for the WOMAC stiffness subscale (p=0.5863), WOMAC total score (p=0.7635), knee cartilage thickness (mean percent change by month 24: 4.5% for SMC021 and 4.1% for placebo, p=0.6743). No treatment effect was observed at month 24 for knee cartilage volume at medial tibial compartment (p=0.9498) and knee cartilage volume at femoral compartment (p=0.2714) or knee cartilage volume (mean percent change by month 24: 2.6% for SMC021 and 3.5% for placebo, p=0.4459).

Pain-killing rescue analgesics were used at some point in the study by fewer patients in the SMC021 group (74.6% patients) than in the placebo group (80.4% patients).

There was a similar probability to need knee surgery in the signal knee in the SMC021 group: 13 (2.5%) patients in the SMC021 group versus 12 (2.4%) patients in the placebo group.

The proportion of responders based on the OMERACT-OARSI definition was slightly higher in the SMC021 group compared to placebo: 67.0% versus 64.9%, p=0.5844.

No statistically significant differences were seen for biomarkers of cartilage and bone turnover (serum CTX-I, serum osteocalcin, urine CTX I/creatinine, and CTX-II/creatinine).

Safety results: A similar incidence of AEs was observed in the SMC021 group (91.2% patients) and to placebo group (90.4% patients). Notably higher differences between treatment groups were observed for hot flush, gastrointestinal events (nausea, dyspepsia, diarrhea, and abdominal discomfort), erythema and dizziness.

AEs leading to study drug discontinuation occurred with higher incidence in the SMC021 group (13.5%) compared to the placebo group (5.8%), with the most common events in the SMC021 group being nausea (GI disorders), followed by hot flush (vascular disorders),dyspepsia (GI disorders), diarrhea (GI disorders), vomiting (GI disorders) and dizziness (nervous system disorders). The AE profile reflects the known GI and skin tolerability issues with calcitonin administration in patients. These events were not SAEs; the incidence of SAEs was similar for both treatment groups: 14.8% patients in the SMC021 groups and 15.7% for the placebo group.

Four patients died during the study, 3 patients in the SMC021 group (acute myocardial infarction, cardiac arrest and subarachnoid hemorrhage) and 1 patient in the placebo group (malignant melanoma). The deaths were not suspected to be related to the study medication. The incidence of the SOC

neoplasms benign, malignant and unspecified (including cysts and polyps) was similar in both treatment groups: 3.8% patients in the SMC021 group versus 4.1% patients in the placebo group. The most frequently reported treatment emergent AEs in this category were: prostate cancer in 5 patients in the SMC021 group (of 199 men) and 5 patients in the placebo group (of 204 men). The incidence of basal cell carcinoma was similar in both treatment groups. No cases of pituitary adenoma were reported.

Mechanistically it is noteworthy and reassuring that no differences in the occurrence of hypocalcaemia have been observed. No new signs or safety signals emerged from hematology or clinical chemistry (including liver function), renal function, vital signs, weight changes, or ECG.

Conclusion: This study suggests that SMC021 is a generally safe but not effective drug for the treatment in OA. While SMC021 administration appears to be generally safe it does have a GI tolerability profile which leads to some early discontinuations.

The present study was not able to reproduce the positive findings of study CSMC021C2301 as it could not confirm any of the previously identified statistically significant efficacy benefits of SMC021 over placebo. From a structural perspective it appeared that the study population in study CSMC021C2302 was faster progressing and hence more severe than in CSMC021C2301, while baseline pain scores were comparable between both studies.

Date of report: 13 August 2012